Protocol I3Y-MC-JPBX (b)

A Randomized Phase 2 Study of Abemaciclib (LY2835219) versus Docetaxel in Patients with Stage IV Squamous Non-Small Cell Lung Cancer Previously Treated with Platinum-Based Chemotherapy

NCT02450539

Approval Date: 12-Feb-2020

1. Protocol I3Y-MC-JPBX(b)

A Randomized Phase 2 Study of Abemaciclib (LY2835219) versus Docetaxel in Patients with Stage IV Squamous Non-Small Cell Lung Cancer Previously Treated with Platinum-Based Chemotherapy

Abemaciclib (LY2835219)

Study JPBX is a multicenter, randomized, open-label, parallel, comparator-controlled, Phase 2 trial in Stage IV squamous non-small cell lung cancer patients who have progressed after platinum-based chemotherapy, evaluating second-line treatment with abemaciclib versus docetaxel.

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Protocol Approved by Lilly: 27 March 2015
Amendment (a) Approved by Lilly: 08 February 2019
Amendment (b) Electronically Signed and Approved by Lilly on date provided below.

Approval Date: 12-Feb-2020 GMT

2. Synopsis

Study Rationale

Patients with metastatic non-small cell lung cancer (NSCLC) with squamous histology have a poor overall survival compared to NSCLC patients with adenocarcinoma histology. Squamous cancer cells are correlated with a loss of $p16^{INK4a}$ methylation and an absence of Kirsten rat sarcoma (*KRAS*) mutations. The $p16^{INK4A}$-cyclin D-cyclin-dependent kinases 4 and 6 (CDK 4 and 6) - retinoblastoma pathway is frequently dysregulated in NSCLC, including squamous histology, and therefore represents an attractive therapeutic target (Zhou et al. 2001). Abemaciclib is a potent and selective small molecule inhibitor of CDK4 and 6 that has shown acceptable safety/tolerability as well as evidence of clinical activity in multiple tumor types.

The Phase 2 Study I3Y-MC-JPBX (JPBX) will evaluate the clinical activity of abemaciclib versus docetaxel therapy with respect to investigator-assessed progression-free survival (PFS) in patients with Stage IV squamous cell carcinoma NSCLC who have relapsed after prior platinum-based therapy for advanced disease.

Clinical Protocol Synopsis: Study I3Y-MC-JPBX

Name of Investigational Product: Abemaciclib (LY2835219)	
Title of Study: A Randomized Phase 2 Study of Abemaciclib (LY2835219) versus Docetaxel in Patients with Stage IV Squamous Non-Small Cell Lung Cancer Previously Treated with Platinum-Based Chemotherapy	
Number of Planned Patients: 150 Entered: 195 Enrolled/Randomized: 150 Completed: 150	**Phase of Development:** 2
Length of Study: Approximately 21 months Planned first patient visit: June 2015 Planned last patient visit: February 2017	

Objectives: The primary objective of this study is to compare treatment with abemaciclib versus docetaxel therapy with respect to investigator-assessed progression-free survival (PFS) in patients with Stage IV squamous cell carcinoma NSCLC who have relapsed after prior platinum-based therapy for advanced disease.
 	
The secondary objectives of the study are:
 	
• To evaluate the pharmacokinetic (PK) parameters including abemaciclib and its active metabolites
• To compare treatment of abemaciclib versus docetaxel with respect to the following:
 	
   • Overall survival (OS)
   • Overall response rate (ORR) [complete response (CR) + partial response (PR)]
   • Disease control rate (DCR) [CR + PR + stable disease]
   • Time to worsening of Performance Status (PS)
   • The safety and tolerability using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0
   • Change from baseline in patient-reported outcomes including: 1) the MD Anderson Symptom Inventory Lung Cancer (MDASI-LC) questionnaire pain and disease-related symptoms scores; and 2) the EuroQol Group's EQ-5D-5L questionnaire index score, derived from the 5-item descriptive system, and visual analog scale (VAS) self-rated health score.	

The exploratory objectives are:

- To explore potential biomarkers related to the cell cycle pathway components, abemaciclib, and/or the pathogenesis of lung cancer, and their associations with clinical outcomes
- To explore the relationship between abemaciclib exposure and response
- To explore if change in tumor size is associated with PFS and OS

Study Design: Study I3Y-MC-JPBX is a multicenter, randomized, open-label, parallel, comparator-controlled, Phase 2 trial in Stage IV squamous NSCLC patients who have progressed after platinum-based chemotherapy, evaluating treatment with abemaciclib versus docetaxel. The study will enroll approximately 150 patients in 2:1 randomization (100 patients in abemaciclib and 50 patients in docetaxel). Patients will be stratified at randomization according to the following: Eastern Cooperative Oncology Group (ECOG) PS (0 vs. 1); number of prior therapies (received only platinum-based therapy vs. platinum-based therapy plus immune checkpoint inhibitor); and time since the initiation of first-line therapy ($\leq$ 9 vs. >9 months).

Diagnosis and Main Criteria for Inclusion and Exclusions: Patients are eligible to be included in the study if they meet following criteria: [1] have confirmed diagnosis of Stage IV NSCLC disease of predominantly squamous histology; [2] availability of adequate formalin-fixed paraffin-embedded tumor-derived material (tumor blocks or slides); [3] have progressed during or after one and only one prior first-line platinum-based chemotherapy regimen with or without maintenance therapy for advanced/metastatic disease; [4] have a PS of 0 to 1 on the ECOG scale; [5] have the presence of measurable disease as defined by Response Evaluation Criteria In Solid Tumors (RECIST) Version 1.1; [6] have discontinued all previous treatments for cancer (including chemotherapy, radiotherapy, immunotherapy, and endocrine therapy) prior to receiving study drug, and recovered from the acute effects of therapy; [7] have adequate organ function; [8] are $\geq$ 18 years of age; [9] have agreed contraception methods; [10] have an estimated life expectancy of at least 12 weeks and in the judgment of the investigator will be able to complete at least 2 cycles of treatment; [11] have given written informed consent prior to any study-specific procedures; [12] are reliable and willing to make themselves available for the duration of the study and are willing to follow study procedures; and [13] are able to swallow capsules or tablets.

Patients will be excluded from the study if they meet any of the following criteria: [14] are currently receiving an investigational drug in a clinical trial or participating in any other type of medical research judged not to be scientifically or medically compatible with this study; [15] have known or suspected allergy to docetaxel or any of its components; [16] have received treatment with a drug that has not received regulatory approval for any indication; [17] have received prior treatment with any CDK 4 and 6 inhibitor; [18] have had major surgery (excluding biopsy) < 28 days of the initial dose of study drug and/or have not recovered from the acute effects of the surgery; [19] have a personal history of any of the following conditions: syncope of either unexplained or cardiovascular etiology, ventricular tachycardia, ventricular fibrillation, or sudden cardiac arrest; [20] have serious preexisting medical conditions that, in the judgment of the investigator, would preclude participation in this study; [21] have a history of any other cancer (except non-melanoma skin cancer or carcinoma in-situ of the cervix), unless in complete remission with no therapy; [22] have the presence of unstable central nervous system metastasis; [23] have active bacterial, fungal, and/or known viral infection; or [24] are female, pregnant and lactating women; unwilling to use medically effective birth control method.

Test Product, Dosage, and Mode of Administration: Abemaciclib 200 mg orally every 12 hours on Days 1 to 21 of a 21-day cycle

Reference Therapy, Dose, and Mode of Administration: Docetaxel 75 mg/m^2 intravenous infusion on Day 1 of a 21-day cycle

Planned Duration of Treatment:

Treatment period: until disease progression or unacceptable toxicity occurs (or both)

Short-term follow-up (postdiscontinuation): 30 days

Long-term follow-up (postdiscontinuation): until death

Criteria for Evaluation:

Efficacy:

- Efficacy assessments include imaging studies/tumor assessments, according to RECIST v. 1.1, performed every 6 weeks, and survival.

    · PFS
    · OS
    · Overall Response Rate
    · DCR
    · Time to worsening ECOG PS

Safety:

- Safety will be evaluated based on recorded adverse events (AEs), physical examinations, vital sign measurements, and clinical laboratory assessments. Adverse events and clinical lab values will be coded using NCI CTCAE Version 4.0.

Health Outcomes:

- Health outcomes will be assessed using standardized instruments, MDASI-LC and EQ-5D-5L. Investigators will report resource utilization such as concomitant medications, transfusions, radiation therapy, surgery, and treatment-related hospitalization days.

Pharmacokinetics:

- The plasma concentrations of abemaciclib and its metabolites LSN2839567 and LSN3106726 will be measured for patients receiving abemaciclib. Covariate effects (such as age, weight, sex, and plasma protein levels) on the PK parameters of abemaciclib in plasma will also be investigated.

Biomarkers:

- Whole blood, plasma, and tissue samples will be tested for biomarkers relevant to the cell cycle pathway, abemaciclib, docetaxel, and/or the pathogenesis of lung cancer and to correlate these markers to clinical outcomes.

Statistical Methods:

Statistical: This study will enroll approximately 150 patients in 2:1 randomization (100 patients in abemaciclib and 50 patients in docetaxel). The primary PFS analysis will be performed after 120 PFS events are observed. Historical information will be incorporated into the control arm during the primary analysis by using a Bayesian approach. Assuming a hazard ratio (HR) of 0.64, with 150 patients and the proposed Bayesian design, power of 90.5% was estimated by simulation. Under a frequentist design, this sample size yields roughly 75% power with 1-sided type I error of 0.05. If the true median PFS for the docetaxel arm is 3 months, the HR of 0.64 amounts to an approximately 1.7-month improvement in median PFS for the abemaciclib arm under an additional assumption of exponential survival distribution.

Efficacy: Efficacy analyses will be based on the intention-to-treat (ITT) analysis set. This population is defined as all patients randomized to study treatment. The primary method of analysis for comparing PFS between the treatment arms will use a Bayesian exponential-likelihood model with a hierarchical random-effects distribution on treatment effects. In addition to the primary analysis of PFS, the following analysis will be conducted based on observed PFS data: 1) A stratified log-rank test (stratified using the same factors as the randomization scheme) will be used to compare the PFS distribution between treatment groups. 2) The Kaplan-Meier method will be used to estimate the PFS curve for each treatment group. 3) The Cox proportional hazard model will be used to estimate treatment HR and corresponding 95% confidence interval.

Safety: All safety summaries and analyses will be based upon the Safety Population as defined as all enrolled patients receiving at least 1 dose of any study drug. Overall exposure to study drug, the numbers of patients completing each cycle, and the dose intensity will be summarized using descriptive statistics. An overall summary of AEs will be provided for AEs deemed by the investigator to be possibly related to study drug, and repeated for events regardless of study drug causality. Incidence rates of these events will be compared between treatment arms using Chi-square test.

Health Outcomes: The MDASI-LC will be summarized for each assessment period. EQ-5D 5L responses for each item will be summarized by frequency and corresponding percentages. Descriptive statistics for the index and VAS will be calculated.

Pharmacokinetics: Mean population PK parameters for abemaciclib in plasma (clearance, exposure, volume of distribution, and half-lives) and inter-individual PK variability will be computed using nonlinear mixed effect modeling (NONMEM).

Pharmacodynamics: Pharmacodynamic (PD) data (such as neutrophil, lymphocytes, or platelets counts in blood, etc.) collected in this study may be analyzed by means of NONMEM and connected to the population PK model in a PK/PD model.

Biomarkers: Correlative analyses will be performed to investigate the associations between biomarkers and clinical outcomes.

3. Table of Contents

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4.   Abbreviations and Definitions

Term	Definition
AE	adverse event
	Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.
ALK	anaplastic lymphoma kinase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
assent	Agreement from a child or other individual who is not legally capable of providing consent, but who can understand the circumstances and risks involved in participating in a study (required by some institutional review boards [IRBs]).
AST	aspartate aminotransferase
Audit	A systematic and independent examination of the trial-related activities and documents to determine whether the evaluated trial-related activities were conducted, and the data were recorded, analyzed, and accurately reported according to the protocol, applicable standard operating procedures (SOPs), good clinical practice (GCP), and the applicable regulatory requirement(s).
BAC	Bayesian Augmented Control
BSC	best supportive care
CDK	p16INK4A-cyclin D-cyclin-dependent kinases
CI	confidence interval
CNS	central nervous system
collection database	A computer database where clinical trial data are entered and validated.
companion diagnostic	An in vitro diagnostic device (assay or test) that provides information that is essential for the safe and effective use of a corresponding therapeutic product

complaint	A complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety or effectiveness, or performance of a drug or drug delivery system.
compliance	Adherence to all the trial-related requirements, good clinical practice (GCP) requirements, and the applicable regulatory requirements.
continued access period	The period between study completion and end of trial during which patients on [investigational product[s] or study treatment] who continue to experience clinical benefit and no undue risks may continue to receive [investigational product[s] or study treatment] until one of the criteria for discontinuation is met.
CR	complete response
CrCl	creatinine clearance
CRF/eCRF	case report form/electronic case report form Sometimes referred to as clinical report form: A printed or electronic form for recording study participants' data during a clinical study, as required by the protocol.
CRP	clinical research physician Individual responsible for the medical conduct of the study. Responsibilities of the CRP may be performed by a physician, clinical research scientist, global safety physician, or other medical officer.
CSR	clinical study report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DCR	disease control rate
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EGFR	epidermal growth factor receptor
end of trial	End of trial is the date of the last visit or last scheduled procedure for the last patient.

enroll	The act of assigning a patient to a treatment. Patients who are enrolled in the trial are those who have been assigned to a treatment.
enter	Patients entered into a trial are those who sign the informed consent form directly or through their legally acceptable representatives.
EQ-5D-5L	EuroQol 5 Dimension 5 Level
ERB	ethical review board
	A board or committee (institutional, regional, or national) composed of medical and nonmedical members whose responsibility is to verify that the safety, welfare, and human rights of the patients participating in a clinical trial are protected.
FFPE	formalin-fixed paraffin-embedded
GCP	good clinical practice
G-CSF	granulocyte-colony stimulating factor
HIV	human immunodeficiency virus
HR	hazard ratio
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
ILD	interstitial lung disease
IND	Investigational New Drug application
Informed consent	A process by which a patient voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the patient's decision to participate. Informed consent is documented by means of a written, signed, and dated informed consent form.
interim analysis	An interim analysis is an analysis of clinical trial data, separated into treatment groups, that is conducted before the final reporting database is created/locked.
investigational product (IP)	A pharmaceutical form of an active ingredient substance or placebo being tested, or used as a reference, in a clinical trial

investigator	A person responsible for the conduct of the clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the principal investigator.
ITT	intention-to-treat
	The principle that asserts that the effect of a treatment policy can be best assessed by evaluating on the basis of the intention to treat a patient (that is, the planned treatment regimen) rather than the actual treatment given. It has the consequence that patients allocated to a treatment group should be followed up, assessed, and analyzed as members of that group irrespective of their compliance to the planned course of treatment.
IUD	intrauterine device
IV	intravenous
IWRS	interactive web-response system
KRAS	Kirsten rat sarcoma
legal representative	An individual, judicial, or other body authorized under applicable law to consent on behalf of a prospective patient to the patient's participation in the clinical study.
Lilly Safety System	Global safety database that tracks and reports serious adverse and spontaneous events occurring while using a drug/drug delivery system.
LLT	Lower Level Term
MATE	multidrug and toxin extrusion protein
MDASI-LC	MD Anderson Symptom Inventory – Lung Cancer
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NCI	National Cancer Institute
NONMEM	nonlinear mixed effect modeling
NSCLC	non-small cell lung cancer
ORR	overall response rate

OS	overall survival
patient	A study participant who has the disease or condition for which the investigational product is targeted.
PD	progressive disease
PET	positron emission tomography
PK	pharmacokinetic
PK/PD	Pharmacokinetic/pharmacodynamic
PFS	progression-free survival
PO	orally
PR	partial response
PRO	patient-reported outcome
PS	performance status
PT	Preferred Term
Q12H	every 12 hours
QoL	quality of life
QTc	corrected QT interval
RANK-L	nuclear factor kappa B ligand
randomize	the process of assigning patients to an experimental group on a random basis
Rb	retinoblastoma
RECIST	Response Evaluation Criteria in Solid Tumors
reporting database	A point-in-time copy of the collection database. The final reporting database is used to produce the analyses and output reports for interim or final analyses of data.
re-screen	to screen a patient who was previously declared a screen failure for the same study
SAE	serious adverse event

SAP	Statistical Analysis Plan
screen	The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical study. In this study, screening involves invasive or diagnostic procedures and/or tests (for example, diagnostic psychological tests, x-rays, blood draws). Informed consent for these screening procedures and/or tests shall be obtained.
screen failure	patient who does not meet one or more criteria required for participation in a trial
SD	stable disease
SmPC	Summary of Product Characteristics
SOC	System Organ Class
Study completion	This study will be considered complete after the final analysis of overall survival is performed.
SUSARs	suspected unexpected serious adverse reactions
TBL	total bilirubin
TEAE	treatment-emergent adverse event
	Any untoward medical occurrence that either occurs or worsens at any time after treatment baseline and that does not necessarily have to have a causal relationship with this treatment.
TKI	tyrosine kinase inhibitor
ULN	upper limits of normal
US	United States
VAS	visual analog scale
VTE	venous thromboembolic event

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5. Introduction

5.1. Lung Cancer

Lung cancer is the most common cancer worldwide, with an estimated 1.6 million new cases per year, and the leading cause of cancer-related mortality with an estimated 1.4 million cancer-related deaths per year (Bray et al. 2012; Bunn 2012). The majority of lung cancer cases (approximately 85%) consist of non-small cell lung cancer (NSCLC), with 65% to 75% of cases presenting as Stage III or Stage IV (SEER 1975-2006; Ihde 1992; Shepherd et al. 1993; Walling 1994). Lung cancer can further be classified into histology subtypes: nonsquamous carcinoma, which includes adenocarcinoma that accounts for approximately 40% of NSCLCs, large cell carcinoma, and other cell types; and squamous (30%) (McKeage et al. 2010; Piperdi et al. 2014). Important differences exist between major subtypes of NSCLC that have prognostic and predictive value of differential response rate, overall survival (OS), or toxicity profile. Clinical studies have demonstrated that patients with squamous histology have poorer outcomes, with a 1-year survival rate of approximately 14.6% (Simon 2014).

Patients with good performance status (PS) are first generally given platinum-based chemotherapy (Bülzebruck et al. 1992), which is associated with longer survival, improved quality of life (QoL), disease-related symptoms, and PS (Cullen et al. 1988; Socinski et al. 2003; Stinchcombe and Socinski 2009). However, even with treatment, the majority of patients relapse, with a median time to progression of 3 to 6 months after initiating chemotherapy (Schiller et al. 2002; Sandler et al. 2006; Stinchcombe and Socinski 2009). Recent clinical trials suggest that approximately 40% to 50% of patients are eligible for second-line chemotherapy (Socinski et al. 2002; Sandler et al. 2006).

Currently approved second-line standard of care treatments for NSCLC consist of monotherapy with pemetrexed, erlotinib, or docetaxel (Hanna et al. 2004; Shepherd et al. 2005). Second-line treatment outcomes remain poor, with an overall response rate (ORR) of less than 10% and median OS of 7 to 9 months (Garon et al. 2014). Ramucirumab was recently approved in the United States (US) for treatment of NSCLC in combination with docetaxel in patients that have relapsed after initial platinum-based therapy. Those with squamous histology have challenges for treatment options because of the lack of driver mutations associated with response to approved agents (Garon et al. 2014).

5.1.1. Second-Line Treatment Options

Pemetrexed: Pemetrexed is indicated as single-agent second-line treatment chemotherapy for locally advanced or metastatic nonsquamous NSCLC (Alimta, US package insert, 2013). In an open-label randomized Phase 3 study of pemetrexed versus docetaxel in patients that have

relapsed after first-line platinum-based therapy, pemetrexed demonstrated similar efficacy to docetaxel in respect to median survival (8.3 vs. 7.9 months) and progression-free survival (PFS) (2.9 vs. 2.9 months) (Hanna et al. 2004). A retrospective analysis of NSCLC subtypes demonstrated that patients with squamous cell histology demonstrated a median OS of 6.2 months with pemetrexed compared to 7.4 months for docetaxel (Scagliotti et al. 2009).

EGFR TKIs

Erlotinib, an epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI), is indicated for the treatment of patients with locally advanced or metastatic NSCLC after failure of at least 1 prior chemotherapy regimen (Tarceva US package insert, 2010). In the BR.21 study, a double blind, placebo-controlled trial, erlotinib was evaluated in NSCLC patients that had failed first-line or second-line chemotherapy treatments. The median PFS was 2.2 months in the erlotinib arm compared to 1.8 months in the placebo group (adjusted hazard ratio [HR]; 0.61; 95% confidence interval [CI]: 0.51, 0.74; p<0.001). The erlotinib group had a median OS of 6.7 months compared to 4.7 months for the control group (HR 0.70; 95% CI: 0.58, 0.85; p<0.001) (Shepherd et al. 2005).

Geftinib, another first-generation EGFR TKI, has been registered for advanced NSCLC for any line in patients with tumors expressing activating *EFGR*-mutation. In the ISEL trial, geftinib failed to show improved survival in chemotherapy-refractory patients compared to placebo; however, survival was significantly improved in the subset of Asian origin population (Thatcher et al. 2005; Carnio et al 2014). In the INTEREST study comparing geftinib to docetaxel, the trial met its primary endpoint of non-inferiority for survival with a mean OS of 8.0 month compared to 7.9 months in the docetaxel arm (Thatcher et al. 2005; Manegold 2014).

Docetaxel: Docetaxel is approved for the treatment of patients with locally advanced or metastatic NSCLC after failure of prior platinum-based chemotherapy. In the TAX 317 study, docetaxel 75 mg/m^2 administered every 3 weeks demonstrated significant median survival compared to best supportive care (BSC) (7.0 vs. 4.6 months, respectively) (Shepherd et al. 2000). Time to progression was noted to be 12.4 weeks in the docetaxel arm compared to 7 weeks in the BSC arm (Docetaxel label). In the TAILOR study in EGFR wild-type patients after first-line platinum doublet, erlotinib had a median OS and PFS of 5.4 and 2.4 months, respectively. Docetaxel has a medium OS of 8.2 months and median PFS of 2.9 months (Garassino et al. 2013).

Ramucirumab: In the REVEL study, NSCLC patients were randomized to either docetaxel plus ramucirumab or docetaxel monotherapy after receiving first-line platinum based therapy. A total of 1253 patients were randomized, with 628 assigned to ramucirumab plus docetaxel and 625 patients assigned to placebo plus docetaxel, with the squamous population being 157 and 171, respectively. In all subtypes, the median survival was 10.5 months for those receiving ramucirumab plus docetaxel compared to 9.1 months in the control group. A subgroup analysis of patients with squamous histology showed a longer survival for those receiving ramucirumab compared to the control arm (9.5 months vs. 8.2 months). Median PFS was 4.5 months for the ramucirumab group compared to 3.0 months for the control group (Garon et al. 2014).

Immunotherapy

Nivolumab, a fully human IgG4 immune checkpoint inhibitor antibody, was recently approved in the US for treatment of patients with advanced (metastatic) squamous NSCLC who have progressed after a platinum-based chemotherapy. Nivolumab works by inhibiting the cellular pathway known as PD-L1 protein on cells that blocks the body's immune system from attacking cancerous cells. In the *CheckMate 017* study, 272 patients received either nivolumab (135 patients) or docetaxel (137 patients). The interim analysis showed a median OS of 9.2 months and 6 months (HR 0.59; 95% CI: 0.44, 0.79; p=0.00025) with nivolumab and docetaxel, respectively. In a Phase 2, single-arm study (CheckMate 063), 117 patients with squamous NSCLC received nivolumab after progressing with a platinum-based therapy and at least one additional systemic regimen (Rizvi et al. 2015). The overall median PFS was 1.9 months (95% CI: 1.8, 3.2) and the median overall survival was 8.2 months (95% CI: 6.1, 10.9) (Rizvi et al. 2015).

5.1.2. Squamous NSCLC

Squamous histology has a worse OS rate compared to those with adenocarcinoma histology (Al-Farsi and Ellis 2014). Additionally, molecular profiles differ between these 2 histology types in respect to mutations of *EGFR* or *V-Ki-ras2* Kirsten rat sarcoma viral oncogene homolog (KRAS) genes. *EGFR* mutations, translocations of anaplastic lymphoma kinase (ALK), and mutations in *KRAS* have been reported largely in adenocarcinoma (nonsquamous) histology subtype (Simon 2014). Squamous cancer cells rarely have mutations in *EGFR* or ALK fusions, and are correlated with a loss of p16^{INK4a} methylation and an absence of *KRAS* mutations (Zhou et al. 2001*)*. Alterations in other receptor tyrosine kinases, such as fibroblast growth factor receptor 1 (20% squamous NSCLC), discoidin domain receptor (4% squamous NSCLC), and TP53 (80% squamous NSCLC), are affected by somatic mutations, and inactivation of CDKN2A and RB1 pathways (79%) have been identified (Shtivelman et al. 2014). Additionally, the 16^{INK4A}-cyclin D-cyclin-dependent kinases 4 and 6 (CDK 4 and 6) - retinoblastoma pathway is frequently dysregulated in NSCLC, including squamous histology, and therefore represents an attractive therapeutic target (Zhou et al. 2001).

5.2. Study Rationale

During the cell cycle, the G1 restriction point controls entry into S phase and is essential for maintaining control of cell division (Sherr 1996; Ortega et al. 2002). CDK 4 and 6 participates in a complex with D-type cyclins to initiate the transition through the G1 restriction point. Cyclin-dependent kinase inhibitors p15^{INK4b} and p16^{INK4a}, the retinoblastoma tumor suppressor protein, and cyclin D family members are among the major regulatory genes of the G_1/S transition. Overexpression of cyclin D1, abnormal RB1 pathway functioning, and mutated or aberrant p16^{INK4a} have been reported in lung cancer (Zhou et al. 2001).

The CDK 4 and 6 - cyclinD complex regulates the G1 restriction point through phosphorylation of the retinoblastoma (Rb) tumor suppressor protein. Alterations in this pathway occur frequently in a broad spectrum of human cancers and involve: 1) loss of cyclin-dependent kinase inhibitors by mutation or epigenetic silencing, 2) mutation/overexpression of either CDK 4 and 6

or cyclin D, or 3) inactivation of Rb. With the possible exception of those tumors with complete inactivation of Rb, which functions downstream of the CDK 4 and 6 - cyclinD complex, all these cancers are potentially sensitive to pharmacologic inhibition of CDK 4 and 6. From a therapeutic standpoint, the goal of inhibiting CDK 4 and 6 with a small molecule inhibitor is to prevent cell cycle progression through the G1 restriction point, thus arresting tumor growth.

Abemaciclib is a potent and selective small molecule inhibitor of CDK 4 and 6 that has shown acceptable safety/tolerability as well as evidence of clinical activity in multiple tumor types. In the Phase 1 Study I3Y-MC-JPBA (JPBA), abemaciclib has shown acceptable safety/tolerability, as well as evidence of clinical activity in multiple tumor types. In addition, Study JPBA included a NSCLC expansion cohort of 68 patients with any histology subtype that was advanced and/or metastatic. Two of the 68 patients (1 nonsquamous *KRAS* mutant and 1 squamous) had a partial response (PR). Among the remaining patients, 31 (45.6%) had stable disease (SD), 16 (23.5%) had progressive disease (PD), and 19 (27.9%) were not evaluable. Nine patients were squamous NSCLC. Within the squamous population, one patient achieved a PR. The disease control rate (DCR) [PR+SD] was 55% (5 patients), with 33% (3 patients) having a DCR for 24 or more weeks. Clinical activity was noted in both histologies with abemaciclib.

Limited treatment options exist for patients with squamous NSCLC compared to those with nonsquamous histology, with docetaxel being the standard of care for this patient population in the second-line setting. However, docetaxel has modest improvement in PFS (2.9 months) while adding significant toxicity in the advanced population. Abemaciclib appears to have single-agent activity based upon preliminary efficacy data and a safety profile that is manageable and amenable to chronic administration.

More information about the known and expected benefits, risks and reasonably anticipated adverse events (AEs) of abemaciclib may be found in the Investigator's Brochure (IB). Information on AEs expected to be related to the study drug may be found in Section 7 (Development Core Safety Information) of the IB. Information on serious adverse events (SAEs) expected in the study population independent of drug exposure and that will be assessed by the sponsor in aggregate, periodically during the course of the study, may be found in Section 6 (Effects in Humans) of the IB.

More detailed information about the known and expected benefits and risks of docetaxel may be found in the following: Package Insert and Summary of Product Characteristics (SmPC).

5.3.   Rationale for Amendment (a)

Study JPBX protocol was amended to update the dosing guidance for cases of nonhematologic toxicity, diarrhea, and ALT increase. This amendment will harmonize the dosing guidance across all clinical trials of abemaciclib in the metastatic setting. The amendment updated the safety language regarding hepatic monitoring, assessment of renal function, and venous thromboembolic events (VTEs) for ongoing patients. Minor typographical and formatting edits were made throughout the document for clarity and consistency.

5.4. Rationale for Amendment (b)

Study JPBX protocol was amended to update the safety monitoring and guidance for interstitial lung disease (ILD)/pneumonitis. Changes to the dose adjustment and delay section and Table JPBX.9.2 were done to specify dose modifications in response to ILD/pneumonitis events. These updates are in alignment with changes made in the development core safety information of the IB.

The protocol was updated to bring references to abemaciclib into alignment with the sponsor's standard language.

Section 9.6 (Concomitant Therapy) was updated to align with the current IB. Additional language was added cautioning against concomitant use of abemaciclib and substrates of the following:

- P-glycoprotein
- breast cancer resistance protein
- organic cation transporter 2
- multidrug and toxin extrusion protein 1 (MATE1), and
- MATE2-K

Substrates of these transporters, including metformin, digoxin, and dofetilide, should be substituted or avoided.

The Concomitant Therapy (Section 9.6) was also updated to remove cautionary language regarding coadministration of narrow therapeutic index CYP substrate drugs. This is based on a clinical study (Study I3Y-MC-JPCB) which found no meaningful effect of abemaciclib on the pharmacokinetics of CYP substrates, namely caffeine [CYP1A2], S-warfarin [CYP2C9], midazolam [CYP3A], and dextromethorphan [CYP2D6].

The list of Inducers and Strong Inhibitors of CYP3A (Attachment 10) was also modified to reflect updated guidance.

Minor typographical and formatting edits were made throughout the document for clarity and consistency.

6. Objectives

6.1. Primary Objective

The primary objective of this study is to compare treatment with abemaciclib versus docetaxel therapy with respect to investigator-assessed PFS in patients with Stage IV squamous cell carcinoma NSCLC who have relapsed after prior platinum-based therapy for advanced disease.

6.2. Secondary Objectives

The secondary objectives of the study are as follows:

- To evaluate the pharmacokinetic (PK) parameters including abemaciclib and its active metabolites

- To compare treatment of abemaciclib versus docetaxel with respect to the following:

  • Overall survival (OS)

  • Overall response rate (ORR) [complete response (CR) + partial response (PR)]

  • Disease control rate (DCR) [CR + PR + stable disease (SD)]

  • Time to worsening of Performance Status (PS)

  • The safety and tolerability using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE version 4.0)

  • Change from baseline in patient-reported outcomes (PROs), including: 1) the MD Anderson Symptom Inventory Lung Cancer (MDASI-LC) questionnaire pain and disease-related symptoms scores; and 2) the EuroQol Group's EQ-5D-5L questionnaire index score, derived from the 5-item descriptive system, and visual analog scale (VAS) self-rated health score.

6.3. Exploratory Objectives

- To explore potential biomarkers related to the cell cycle pathway components, abemaciclib, and/or the pathogenesis of lung cancer, and their associations with clinical outcomes

- To explore the relationship between abemaciclib exposure and response

- To explore if change in tumor size is associated with PFS and OS

7. Study Population

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened. Each time re-screening is performed, the individual must sign a new informed consent form (ICF) and will be assigned a new identification number.

The following patients may be eligible for rescreening if any of the following circumstances:
- Patients who have become eligible to enroll in the study as the result of a protocol amendment.
- Patient status has changed such that the eligibility criterion that caused the patient to screen fail would no longer cause the patient to screen fail again.
- Patients who complete screening and meet all inclusion and exclusion requirements but are unable to be enrolled due to extenuating circumstances (such as severe weather, death in family, or child illness).

The investigator should contact the Lilly clinical research physician (CRP) prior to re-screening a patient.

Prospective approval of protocol deviations to recruitment and enrollment criteria (also known as protocol waivers or exemptions) is not permitted.

7.1. Inclusion Criteria

Patients are eligible to be included in the study only if they meet **all** of the following criteria:

[1] have confirmed diagnosis of Stage IV NSCLC disease predominantly squamous histology according to the American Joint Committee on Cancer on Cancer Staging Handbook (Edge et al. 2009). Squamous NSCLC diagnosis must be confirmed by histology or cytology local pathology report.

[2] have availability of adequate formalin-fixed paraffin-embedded (FFPE) tumor-derived material (tumor blocks or 10 slides minimum) from a core needle biopsy or surgery for analysis of *biomarkers*. This sample should be the most recent available sample containing adequate material. Re-biopsy after progression from prior therapy is not required.

[3] have progressed during or after platinum-based chemotherapy regimen for advanced disease

- Patients may have received one additional line of therapy only if an immune checkpoint inhibitor was administered (for example, nivolumab). This prior immunotherapy is allowed and does count as prior therapy. No other anticancer agents (for example, chemotherapy, radiotherapy) are permitted as prior therapy.

- Patients with recurrent disease after adjuvant or neoadjuvant therapy or patients who have received combined chemotherapy and radiation for locally advanced disease are eligible, if:

      a. The patient has progressed within 6 months after completion of adjuvant or neoadjuvant platinum-based therapy (adjuvant therapy will be considered the patient's one and only prior first-line, platinum-based chemotherapy). The time from completion of the last cycle of adjuvant or neoadjuvant therapy to progression must be less than 6 months. For radiotherapy for locally advanced disease with curative intent with chemotherapy (platinum-based therapy), the time of completion of chemotherapy or radiotherapy, whichever finishes last, to progression must be less than 6 months to count as a line of therapy.

- May not have received docetaxel as monotherapy or in combination with platinum therapy in first-line setting, or in the neoadjuvant/adjuvant setting

      a. Prior paclitaxel therapy as monotherapy or in combination is permitted (for example, single-agent neoadjuvant/adjuvant setting or combination in first line).

[4] have a performance status (PS) of 0 to 1 on the Eastern Cooperative Oncology Group (ECOG) scale (see Attachment 4)

[5] have the presence of measurable disease as defined by the Response Evaluation Criteria In Solid Tumors RECIST 1.1 (Eisenhauer et al. 2009, see Attachment 7)

[6] have discontinued all previous treatments for cancer (including chemotherapy, radiotherapy, immunotherapy, and endocrine therapy) for at least 21 days for myelosuppressive agents; or 14 days for nonmyelosuppressive agents prior to receiving study drug, and recovered from the acute effects of therapy (treatment-related toxicity resolved to baseline) except for residual alopecia

- **Radiation therapy**: Prior radiotherapy to chest is permitted if completed >3 weeks; and prior radiotherapy to the brain is permitted if completed >4 weeks with assessment of stable disease. Patients must have recovered from the acute toxic effects of the radiotherapy treatment prior to the first dose of study treatment.

[7] have adequate organ function, including:

- hematologic: absolute neutrophil count (ANC) $\geq 1.5 \times 10^9$/L, platelets $\geq 100 \times 10^9$/L, and hemoglobin ≥ 9 g/dL. Patients may receive erythrocyte transfusions to achieve this hemoglobin level at the discretion of the investigator. Initial study drug treatment must not begin earlier than the day after the erythrocyte transfusion.

- hepatic: bilirubin ≤ 1.5 times the upper limit of normal (ULN) and alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 3 times ULN. For patients with hepatic metastases, ALT and AST equaling ≤ 5.0 times ULN are acceptable.

- renal: Calculated creatinine clearance ≥50 mL/min (per the Cockcroft-Gault formula or equivalent, see Attachment 5)

[8]   are ≥ 18 years of age

[9]   have agreed contraception methods as follows

[9a] are a man and agree to use a reliable medically approved method of birth control (for example, intrauterine device [IUD], birth control pills, or barrier method) and to not donate sperm during the study and for at least 3 months following the last dose of study drugs(s) or country requirements, whichever is longer]

[9b] are women of child-bearing potential who test negative for pregnancy within 14 days of start of study treatment and agree to use a reliable medically approved method of birth control (for example, IUD, birth control pills, or barrier method) during the study and for 3 months following the last dose of the study drug(s) or country requirements, whichever is longer

[10] have an estimated life expectancy of at least 12 weeks and in the judgment of the investigator, will be able to complete at least 2 cycles of treatment

[11] have given written informed consent prior to any study-specific procedures

[12] are reliable and willing to make themselves available for the duration of the study and are willing to follow study procedures

[13] are able to swallow capsules or tablets

7.2. Exclusion Criteria

Patients will be excluded from the study if they meet **any** of the following criteria:

[14] are currently receiving treatment in a clinical trial involving an investigational product or non-approved use of a drug or device (other than the study drug/device used in this study), or concurrently enrolled in any other type of medical research judged not to be scientifically or medically compatible with this study

[15] have known or suspected allergy to docetaxel or any of its components

[16] have received treatment with a drug that has not received regulatory approval for any indication within 14 or 21 days of the initial dose of study drug of nonmyelosuppressive or myelosuppressive agent, respectively

[17] have received prior treatment with any CDK 4 and 6 inhibitor (or participated in any CDK 4and 6 inhibitor clinical trial for which treatment assignment is still blinded)

[18] have had major surgery (excluding biopsy) < 28 days of the initial dose of study drug and/or have not recovered from the acute effects of the surgery

[19] have a personal history within the last 12 months of any of the following conditions: syncope of either unexplained or cardiovascular etiology, ventricular tachycardia, ventricular fibrillation, or sudden cardiac arrest.

[20] have serious preexisting medical conditions that, in the judgment of the investigator, would preclude participation in this study (for example, history of major surgical resection involving the stomach or small bowel)

[21] have a history of any other cancer (except non-melanoma skin cancer or carcinoma in-situ of the cervix), unless in complete remission with no therapy for a minimum of 3 years

[22] have the presence of unstable central nervous system (CNS) metastasis:

- History of CNS metastasis or stable CNS metastases are allowed (no longer requiring active therapy such as steroid medications). Patients with symptoms of CNS involvement or a history of CNS metastasis will have brain scan during baseline procedures to document stability. Patients having prior brain scan within 45 days of starting therapy and without symptoms of CNS metastases (stable or unstable) do not need to repeat scan at baseline (within 28 days of starting study treatment).

- Steroidal treatment (if indicated) should be completed after cranial irradiation (whole brain radiation therapy, focal radiation therapy, and stereotactic radiosurgery)

- Prior radiotherapy to the brain must be completed ≥ 4 weeks prior to randomization with assessment of stable disease.

- Prior surgical resection should be performed at least 28 days prior to randomization. The patient may have no evidence of Grade ≥ 1 CNS hemorrhage based on pretreatment magnetic resonance imaging (MRI) or intravenous (IV) contrast computed tomography (CT) scan (performed within 28 days before starting study treatment).

[23] have active bacterial, fungal, and/or known viral infection (for example, human immunodeficiency virus [HIV] antibodies, hepatitis B surface antigen, or hepatitis C antibodies). Screening for active infections is not required for enrollment.

[24] females who are pregnant or lactating

7.2.1. Rationale for Exclusion of Certain Study Candidates

Exclusion Criterion [19] is necessary because the effects of abemaciclib on corrected QT (QTc) prolongation are unknown; these conditions may put the patient at additional risk.

Exclusion Criterion [22] is necessary because patients with unstable CNS metastasis are not likely to receive sufficient study treatment, preventing a full assessment of the agents administered in this study. Exclusion Criterion [24] is necessary because the effects of abemaciclib on the developing fetus are unknown.

7.3. Discontinuation

If a patient withdraws informed consent, he or she must not be contacted unless he or she has explicitly provided permission and consent. Lilly may continue to use previously collected medical research data prior to the withdrawal consistent with the original authorization.

7.3.1. Discontinuation of Inadvertently Enrolled Patients

The criteria for enrollment must be followed explicitly. If the investigator site identifies a patient who did not meet enrollment criteria and who was inadvertently enrolled, the sponsor must be notified. If the sponsor identifies a patient who did not meet enrollment criteria and who was inadvertently enrolled, the investigator site will be notified. A discussion must occur between the sponsor CRP and the investigator to determine whether the patient may continue in the study, with or without study drug. Inadvertently enrolled patients may be maintained in the study and on study drug when the Lilly CRP agrees with the investigator that it is medically appropriate for that patient. The patient may not continue in the study with or without study drug if the Lilly CRP does not agree with the investigator's determination it is medically appropriate for the patient to continue. The investigator must obtain documented approval from the Lilly CRP to allow the inadvertently enrolled patient to continue in the study with or without study drug.

7.3.2. Discontinuation of Study Drug

Patients will be discontinued from study drug in the following circumstances:
- disease progression as defined by RECIST v. 1.1
- unacceptable toxicity
- the patient has had 2 dose reductions and experiences an AE that would cause a third dose reduction
- the patient is significantly noncompliant with study procedures and/or treatment
- enrollment in any other clinical trial involving an investigational product or enrollment in any other type of medical research judged not to be scientifically or medically compatible with this study
- investigator decision
  - o the investigator decides that the patient should be discontinued from the study or study drug for any reason (for example, the patient becomes pregnant)
  - o if the patient, for any reason, requires treatment with another therapeutic agent that has been demonstrated to be effective for treatment of the study indication, discontinuation from the study drug occurs prior to introduction of the new agent
- patient decision
  - o the patient or the patient's designee (for example, legal guardian) requests to be withdrawn from the study or study drug

- sponsor decision
  - Lilly stops the study or stops the patient's participation in the study for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and good clinical practice (GCP)

The reason for and date of discontinuation will be collected for all patients. All randomized patients who discontinue regardless of whether or not they received study drug will have procedures performed as shown in the Study Schedule (Attachment 1).

7.3.3. Discontinuation from the Study

Patients will be discontinued from the study in the following circumstances:

- the investigator decides that the patient should be discontinued from the study
- the patient or the patient's designee (for example, legal guardian) requests that the patient be withdrawn from the study
- Lilly stops the study or stops the patient's participation in the study for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP

7.3.4. Discontinuation of Study Sites

Study site participation may be discontinued if Lilly, the investigator, or the ethical review board (ERB) of the study site judges discontinuation of study site participation necessary for medical, safety, regulatory, ethical, or other reasons consistent with applicable laws, regulations, and GCP.

7.3.5. Discontinuation of the Study

The study will be discontinued if Lilly judges discontinuation of the study necessary for medical, safety, regulatory, ethical, or other reasons consistent with applicable laws, regulations, and GCP.

8. Investigational Plan

8.1. Summary of Study Design

8.2. Study Design

Study I3Y-MC-JPBX (JPBX) is a multicenter, randomized, open-label, parallel, comparator-controlled, Phase 2 trial in Stage IV squamous NSCLC patients who have progressed after platinum-based chemotherapy for advanced disease, evaluating treatment with abemaciclib versus docetaxel.

Patients will be stratified at randomization according to the following: ECOG PS (0 vs 1); number of prior therapies (received only platinum-based therapy vs. platinum-based therapy plus immune checkpoint inhibitor); and time since the initiation of first-line therapy ($\leq$ 9 vs. >9 months) (Figure JPBX.8.1).

Abbreviations: IV = intravenous; N = number; NSCLC = non-small cell lung cancer; PD = progressive disease; PO = orally; Q12H = every 12 hours; R = randomized.

Figure JPBX.8.1.   Illustration of study design.

Database lock for the primary analysis of the PFS endpoint will occur when approximately 120 investigator-assessed PFS events have been observed. The primary analysis of OS will occur 12 months after last patients have been enrolled. This is to ensure adequate survival data are available at the time of analysis. All patients will be followed for survival information until death or study completion, whichever comes first.

Terms used to describe the periods during the study are defined below:

- **Baseline:** begins when the ICF is signed and ends at the first study treatment (or at discontinuation, if no treatment is given).
- **Study Period:** begins at the first study treatment and ends at study completion. The study period does not include the continued access period.
    - **Study Treatment Period:** begins at the first study treatment and ends when the patient and the investigator agree that the patient will no longer continue study

treatment. The date of this agreement is to be reported on the case report form (CRF) as the Date of Discontinuation from study treatment.

- **Postdiscontinuation Follow-Up:** begins the day after the patient and the investigator agree that the patient will no longer continue study treatment.

    Short-term follow-up begins the day after the patient and the investigator agree that the patient will no longer continue study treatment and lasts approximately 30 days (+0 to 7 days).

    Long-term follow-up begins the day after short-term follow-up is completed and continues until the patient's death or overall study completion.

- **Continued Access Period:** begins after study completion (final OS analysis) and ends at the end of trial (last patient visit for the study). During the continued access period, patients on study treatment who continue to experience clinical benefit and no undue risks may continue to receive study treatment until one of the criteria for discontinuation is met. The continued access period includes continued access follow-up.
    - Continued access follow-up: begins the day after the patient and the investigator agree that the patient will no longer continue treatment in the continued access period and lasts approximately 30 days.

8.2.1. Study Completion and End of Trial

This study will be considered complete (that is, the scientific evaluation will be complete [study completion]) following the final analysis of OS (12 months after enrollment is complete), as determined by Lilly. Investigators will continue to follow the study schedule for all patients until notified by Lilly that study completion has occurred.

"End of trial" refers to the date of the last visit or last scheduled procedure for the last patient (Figure JPBX.8.2). The end of trial occurs after study completion and after the last patient has discontinued study treatment and completed any applicable continued access follow-up.

Abbreviation: OS = overall survival.

Figure JPBX.8.2.   Study period and continued access diagram.

8.2.2. Continued Access Period

Patients receiving treatment with either abemaciclib or docetaxel and experiencing ongoing clinical benefit and no undue risks may continue to receive their current treatment in the continued access period until one of the criteria for discontinuation is met (Section 7.3). Lilly will notify investigators when the continued access period begins.

Patients who are in short-term follow-up when the continued access period begins will continue in short-term follow-up until the 30-day short-term follow-up visit is completed. Long-term follow-up does not apply.

Patients who are in long-term follow-up when the continued access period begins will be discontinued from long-term follow-up.

During the continued access period, all AEs, SAEs, and study drug exposure will be reported on the CRF. Serious adverse events will also be reported to Lilly Global Patient Safety (see Section 10.3.1). In the event that an SAE occurs, Lilly may request additional information (such as local laboratory results, concomitant medications, and hospitalizations) in order to evaluate the reported SAE.

Investigators will perform any other standard procedures and tests needed to treat and evaluate patients; however, the choice and timing of the tests will be at the investigator's discretion. Lilly will not routinely collect the results of these assessments.

8.3. Discussion of Design and Control

A randomized, controlled design is being used in this study. Randomization minimizes systematic bias in the selection and assignment of patients to study treatment and provides justification for inferential statistical methods to be used on data from this study. It is expected that abemaciclib will produce robust safety data and better efficacy outcomes than the control; therefore, a 2:1 randomization has been used in this study. Using an appropriate concurrent control arm enables direct statistical estimation of benefits and harms due to study treatment and minimizes bias in the assessment and interpretation of observed treatment effects. Patients will be stratified for differences in factors thought to be associated with clinical outcomes to further reduce the potential for bias and improve the power of the analyses.

A Bayesian augmented control design is being used in this study. This statistical model enables historical data for the concurrent control group to be used analytically in this prospective study, which improves (frequentist) operating characteristics compared with standard (frequentist) designs (see Attachment 6 for more details).

9. Treatment

9.1. Treatments Administered

The following treatments will be administered in this study:

- Experimental Arm A: Abemaciclib 200 mg orally every 12 hours (Q12H) on Days 1 to 21 of a 21-day cycle
- Control (Standard of Care) Arm B: Docetaxel 75 mg/m^2 intravenous (IV) infusion on Day 1 of a 21-day cycle.

Table JPBX.9.1 shows the treatment regimens.

Table JPBX.9.1.   Treatment Regimens/Dosing Schedule

Regimen	Period/Cycle	Dose
Abemaciclib	Treatment/21-day cycle	200 mg PO Q12H Days 1 to 21 of each cycle
Docetaxel[a,b,c]	Treatment/21-day cycle	75 mg/m^2 IV Day 1 of each cycle

Abbreviations: IV = intravenous; PO = orally; Q12H = every 12 hours.

[a] Patients should be premedicated with corticosteroids such as dexamethasone 16 mg per day (e.g., 8 mg twice a day) for 3 days starting 1 day prior to docetaxel administration in order to reduce the incidence and severity of fluid retention, as well as the severity of hypersensitivity. All premedication administered must be adequately documented in the electronic case report form(eCRF).

[b] Body surface area must be calculated and the docetaxel dose adapted accordingly before each subsequent cycle.

[c] Korean and Taiwan sites will administer docetaxel 60 mg/m^2 IV Day 1 of each cycle.

The investigator or his/her designee is responsible for the following:

- explaining the correct use of the study drug and planned duration of each individual's treatment to the patient, site personnel and/or legal representative,
- verifying that instructions are followed properly,
- maintaining accurate records of study drug dispensing and collection,
- and returning all unused medication to Lilly or its designee at the end of the study.

Note: In some cases, sites may destroy the material if, during the investigator site selection, the evaluator has verified and documented that the site has appropriate facilities and written procedures to dispose clinical trial materials.

Patients will be instructed to contact the investigator as soon as possible if they have a complaint or problem with the study drug so that the situation can be assessed.

9.1.1. Docetaxel

Investigators should consult the manufacturer`s instructions for docetaxel for complete prescribing information and follow institutional procedures for the administration of docetaxel. Docetaxel will be administered as an IV infusion of 75 mg/m^2 over approximately 60 minutes.

For sites in Korea and Taiwan, patients will receive docetaxel at a dose of 60 mg/m^2 as an approximate 60-minute IV infusion.

9.2. Materials and Supplies

Abemaciclib will be supplied by Lilly for oral administration. Abemaciclib should be stored according to the temperature range listed on the product label, and should not be opened, crushed, or chewed.

Docetaxel is a commercially available product. Docetaxel branded or generic is permitted. Investigators should consult the manufacturer's instructions for complete packaging, labeling, storage, and stability information.

All study drug provided by Lilly will be labeled according to local country regulatory requirements. Investigators are responsible for instructing patients to store abemaciclib in the original package provided and to keep all medication out of the reach of children.

Lilly is not responsible for the supply of any premedication required according to docetaxel label.

9.3. Method of Assignment to Treatment

Patients who meet all criteria for enrollment will be randomly assigned to receive either abemaciclib or docetaxel during baseline screening at least 4 days prior to planned Cycle 1 Day 1 to allow premedication for docetaxel to occur per label recommendation. Randomization will be stratified by the following factors:

- ECOG PS at baseline (0 vs. 1)
- time since initiation of first-line therapy ($\leq$ 9 months vs. > 9 months)
- number of prior therapies (received only platinum-based therapy vs. platinum-based therapy plus immune checkpoint inhibitor)

Assignment to treatment groups will be determined by a computer-generated random sequence using an interactive web-response system (IWRS).

9.4. Selection and Timing of Doses

A cycle is defined as a planned treatment interval of 21 days (a delay of a cycle due to holidays, weekends, bad weather, or other unforeseen circumstances will be permitted up to 7 days and not counted as a protocol deviation; refer to Table JPBX.9.4).

Abemaciclib will be taken orally Q12H (±approximately 2 hours) on Days 1 through 21 of a 21-day cycle, for a total of 42 doses per cycle. During all cycles, abemaciclib should be taken at approximately the same times each day. On Cycle 1 Day 8, abemaciclib should be taken at home at least 4 hours prior to the schedule visit time. If a patient misses or vomits a dose, that dose should be omitted. The dose of abemaciclib will be administered in the clinic on Day 1 of each cycle.

Docetaxel will be administered IV in the clinic on Day 1 of every cycle. Body surface area must be calculated and the docetaxel dose adapted accordingly before each subsequent cycle. Applied dosages should be no more than 10% above or below calculated ones. Infusions administered within 3 days before or 7 days after the planned 3-week time point due to administrative or unforeseen circumstances(for example, weekend) will be considered acceptable and are at the discretion of the treating investigator. Patients who require a delay of more than 14 days in starting a new cycle of chemotherapy (> 35-day interval between consecutive cycles) should be removed from treatment.

A patient may continue to receive study drug until he or she meets 1 or more of the specified reasons for discontinuation (as described in Section 7.3).

The first administration of study treatment has to be performed within 28 days of consent and no more than 14 days after randomization during baseline.

9.4.1. Dose Rationale for Abemaciclib from Study JPBA

Selection of 200 mg every 12 hours for assessment during Study JPBX is based on safety, clinical activity, and PK and pharmacodynamic data from patients with NSCLC enrolled in Study JPBA.

Study JPBA is the Phase 1 dose-escalation and tumor cohort-expansion study in advanced cancer patients that included a cohort expansion in NSCLC patients. Findings from the Phase 1 Study JPBA indicate that the abemaciclib single-agent maximum tolerated dose (MTD) of 200 mg administered orally Q12H demonstrates an acceptable safety profile.   The most common treatment-emergent adverse events (TEAEs) possibly related to study drug for patients in Study JPBA included diarrhea, nausea, fatigue, neutropenia, vomiting, leukopenia, thrombocytopenia, anemia, decreased appetite, and blood creatinine increased. The adverse event findings are consistent in those patients in the NSCLC cohort.

Additionally, preliminary analysis of the PK data obtained in Study JPBA for abemaciclib at 150 and 200 mg Q12H suggests that the dose of 200 mg administered every 12 hours yields slightly higher and more consistent steady-state plasma concentration levels for abemaciclib.

In particular, the mean minimum steady-state concentration for abemaciclib is more consistently maintained at a value of approximately 200 ng/mL, which represents a threshold value associated with more robust and sustained CDK 4 and 6 inhibition and cell cycle arrest, as indicated by the decrease in phosphorylated retinoblastoma and topoisomerase II alpha expression measured in skin biopsies.

Collectively, these findings indicate that the MTD of 200 mg orally Q12H demonstrates an acceptable safety profile, evidence of target inhibition and cell cycle arrest in skin, and clinical activity against NSCLC. The dose of 200 mg administered every 12 hours is therefore recommended for further assessment in Study JPBX.

9.4.2. Special Treatment Considerations

9.4.2.1. Dose Adjustments and Delays

Table JPBX.9.2.   Toxicity Dose Adjustments and Delays of Abemaciclib for Study JPBX

Toxicity Type	Dose Adjustment Guidelines	Dose Action	Dose Change
Hematologic Toxicity Section 9.4.2.1.2.1	Grade 3	Dose **MUST** be suspended until toxicity resolves to at least Grade 2	Dose **MAY** be reduced by one dose level - investigator's discretion.
Hematologic Toxicity Section 9.4.2.1.2.1	Recurrent Grade 3	Dose **MUST** be suspended until toxicity resolves to at least Grade 2	Dose **MUST** be reduced by one dose level.
Hematologic Toxicity Section 9.4.2.1.2.1	Grade 4	Dose **MUST** be suspended until toxicity resolves to at least Grade 2	Dose **MUST** be reduced by one dose level.
Hematologic toxicity: If patient requires administration of blood cell growth factors Sections 9.4.2.1.2.1 and 9.6.2.3	Regardless of severity (Use of growth factors according to ASCO Guidelines)	Dose **MUST** be suspended for at least 48 hours after the last dose of blood cell growth factors was administered and until toxicity resolves to at least Grade 2.	Dose **MUST** be reduced by one dose level unless already performed for incidence of toxicity that lead to the use of growth factor.
Nonhematologic Toxicity[a] (except diarrhea, ALT increased, and ILD/Pneumonitis) Section 9.4.2.1.2.2	Persistent or recurrent[b] Grade 2 that does not resolve with maximal supportive measures within 7 days to baseline or Grade 1	Dose **MUST** be suspended until toxicity resolves to either baseline or Grade 1.	Dose **MUST** be reduced by one dose level.
Nonhematologic Toxicity (except diarrhea, ALT increased, and ILD/Pneumonitis) Section 9.4.2.1.2.2	Grade 3 or 4	Dose **MUST** be suspended until toxicity resolves to either baseline or Grade 1.	Dose **MUST** be reduced by one dose level.
Diarrhea Sections 9.4.2.1.2.3 and 9.6.2.2	Grade 2 that does not resolve within 24 hours to at least Grade 1	Dose **MUST** be suspended until toxicity resolves to at least Grade 1.	Dose reduction is **NOT** required.

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Toxicity Type	Dose Adjustment Guidelines	Dose Action	Dose Change
Diarrhea Sections 9.4.2.1.2.3 and 9.6.2.2	Persistent or recurrent[b] Grade 2 that does not resolve with maximal supportive measures or any Grade of diarrhea that requires hospitalization	Dose **MUST** be suspended until toxicity resolves to at least Grade 1.	Dose **MUST** be reduced by one dose level.
Diarrhea Sections 9.4.2.1.2.3 and 9.6.2.2	Grade 3 or 4	Dose **MUST** be suspended until toxicity resolves to at least Grade 1.	Dose **MUST** be reduced by one dose level.
ALT Increased Sections 9.4.2.1.2.4 and 10.3.3.1	Persistent or recurrent[b] Grade 2 (>3.0-5.0×ULN)[c], or Grade 3 (>5.0-20.0×ULN)[d]	Dose **MUST** be suspended until toxicity resolves to baseline or Grade 1.	Dose **MUST** be reduced by 1 dose level.
ALT Increased Sections 9.4.2.1.2.4 and 10.3.3.1	Grade 4 (>20.0×ULN)	Abemaciclib **MUST** be discontinued.	Abemaciclib **MUST** be discontinued.
ALT Increased with increased total bilirubin, in the absence of cholestasis Sections 9.4.2.1.2.4 and 10.3.3.1	Grade 3 increased ALT (>5.0×ULN) with total bilirubin >2×ULN	Abemaciclib **MUST** be discontinued.	Abemaciclib **MUST** be discontinued.
ILD/Pneumonitis Sections 9.4.2.1.2.5 and 10.3.3.4	Grade 2 that persists or recurs despite maximal supportive measures and does not return to baseline or Grade 1 within 7 days	Dose **MUST** be suspended until toxicity resolves to baseline or Grade ≤1.	Dose **MUST** be reduced by 1 dose level.
ILD/Pneumonitis Sections 9.4.2.1.2.5 and 10.3.3.4	Grade 3 or 4	Abemaciclib **MUST** be discontinued.	Abemaciclib **MUST** be discontinued.

Abbreviations: ALT = alanine transaminase; ASCO = American Society of Clinical Oncology; ILD = interstitial lung disease; ULN = upper limit of normal.

Note: MAY = per the investigator's clinical judgment; MUST = mandatory.

[a] Additional guidance for hepatic and renal monitoring is in Sections 10.3.3.1 and 10.3.3.2.

[b] Determination of persistent events will be at the discretion of the investigator. Recurrent toxicity refers to the same event occurring within the next 8 weeks (as measured from the stop date of the preceding event). As a general guidance, based on the risk/benefit balance assessment per the investigator, for a patient who experiences a new episode of Grade 3 hematological toxicity after more than 8 weeks following the last episode of same Grade 3 hematological toxicity, the investigator may consider resuming the patient on the same drug dose should the patient satisfy the following conditions:
- shows stable hematological counts (Grade ≤2) during that timeframe
- has absence of any signs or risk of infection
- is benefiting from study treatment

[c] Note: the patient who presents with no liver metastases at baseline.

[d] Grade 3 ALT increased is a trigger for additional assessments and possibly hepatic monitoring. See Section 10.3.3.1 for additional guidance for hepatic monitoring.

9.4.2.1.1. Abemaciclib Dose Adjustments

Dose adjustments as outlined in Table JPBX.9.3 are allowed both within a cycle and between cycles. Abemaciclib must be reduced sequentially by one dose level.

For patients requiring dose reduction(s), any re-escalation to a prior dose level is permitted only after consultation with the Lilly CRP. After re-escalation, subsequent dose adjustments should be based on the dose of abemaciclib that the patient is currently receiving.

Table JPBX.9.3. **Dose Adjustments of Abemaciclib for Study JPBX**

Dose Adjustment	Oral Dose	Frequency
0	200 mg	Q12H
1	150 mg	Q12H
2	100 mg	Q12H

Abbreviation: Q12H = every 12 hours.

If a patient receiving the 100-mg Q12H dose of abemaciclib requires a further dose reduction, the patient should be discontinued from study treatment. If a patient who, in the judgment of the investigator, is receiving clinical benefit from study therapy and requires further dose reduction than what is outlined in Table JPBX.9.3, then the investigator must discuss with the Lilly CRP prior to any further dose reduction.

9.4.2.1.2. Abemaciclib Dose Delays and Omission

Table JPBX.9.4. **General Dose Delays of Abemaciclib for Study JPBX**

General Dose Delays	Time Permitted for Delay
Delay of a cycle due to holidays, weekends, bad weather, or other unforeseen circumstances	7 days
Toxicity-time for recovery to baseline or at least Grade 1 for nonhematologic and at least Grade 2 for hematologic toxicity	Up to 14 days

The start of a cycle may be delayed to allow sufficient time for recovery from toxicity possibly related to study drug. Patients not recovering from such toxicity within 14 days beyond the last day of the prior cycle will be considered for discontinuation from the study.

9.4.2.1.2.1. Hematologic Toxicity

Before the start of each cycle, hematologic toxicity possibly related to abemaciclib must resolve to either baseline or at least Grade 2.

If a patient experiences Grade 3 hematologic toxicity, then dosing <u>must</u> be suspended (until the toxicity resolves to either baseline or at least Grade 2) and the dose of abemaciclib <u>may</u> be reduced by one dose level as outlined in at the discretion of the investigator as outlined in Table JPBX.9.3. If the patient experiences a recurrent episode of Grade 3 hematologic toxicity,

then dosing <u>must</u> be suspended (until the toxicity resolves to at least Grade 2) and the dose of abemaciclib <u>must</u> be reduced by 1 dose level.

If a patient experiences Grade 4 hematologic toxicity possibly related to abemaciclib, then dosing <u>must</u> be suspended (until the toxicity resolves to either baseline or at least Grade 2) and the dose of abemaciclib <u>must</u> be reduced as outlined in Table JPBX.9.3.

Recurrent toxicity refers to the same event occurring within the next 8 weeks (as measured from the stop date of the preceding event). As a general guidance, based on the risk/benefit balance assessment per the investigator, for a patient who experiences a new episode of Grade 3 hematological toxicity after more than 8 weeks following the last episode of same Grade 3 hematological toxicity, the investigator may consider resuming the patient on the same drug dose should the patient satisfy the following conditions:

- The patient showed stable hematological counts (Grade ≤2) during that timeframe

- In the absence of any signs or risk of infection

- The patient is benefiting from study treatment

If a patient requires administration of blood cell growth factors, the dose of LY2835219 <u>must</u> be suspended for at least 48 hours after the last dose of blood cell growth factors was administered and until toxicity resolves to at least Grade 2, then must be reduced by 1 dose level, if a dose reduction for the specific event necessitating the use of the growth factors has not already occurred.

9.4.2.1.2.2. Nonhematologic Toxicity

Before the start of each cycle, nonhematologic toxicity (except alopecia and fatigue) possibly related to abemaciclib must resolve to either baseline or at least Grade 1.

Refer to Section 9.4.2.1.2.3 for guidance and supportive measures of diarrhea toxicity possibly related to abemaciclib, Sections 9.4.2.1.2.4 and 10.3.3.1 for additional hepatic safety and monitoring guidance, and Sections 9.4.2.1.2.5 and 10.3.3.4 for ILD/pneumonitis guidance. If a patient experiences ≥Grade 3 nonhematologic toxicity (except diarrhea, refer to Section 9.4.2.1.2.3; ALT increased, refer to Sections 9.4.2.1.2.4 and 10.3.3.1; ILD/pneumonitis, refer to Sections 9.4.2.1.2.5 and 10.3.3.4) possibly related to abemaciclib, then dosing must be suspended (until the toxicity resolves to either baseline or at least Grade 1) and the dose of abemaciclib must be reduced as outlined in Table JPBX.9.3.

If a patient experiences persistent or recurrent Grade 2 nonhematologic toxicity (except diarrhea, refer to Section 9.4.2.1.2.3; ALT increased, refer to Sections 9.4.2.1.2.4 and 10.3.3.1; ILD/pneumonitis, refer to Sections 9.4.2.1.2.5 and 10.3.3.4) possibly related to abemaciclib that does not resolve with maximal supportive measures within 7 days to either baseline or Grade 1, then dosing <u>must</u> be suspended (until the toxicity resolves to either baseline or at least Grade 1) and the dose of abemaciclib <u>must</u> be reduced as outlined in Table JPBX.9.3.

9.4.2.1.2.3.   Diarrhea

A patient experiencing diarrhea requiring hospitalization (irrespective of grade; that is, requiring IV rehydration) or severe diarrhea (Grade 3 or 4; see Section 9.6.2.2 and Attachment 11) must have study treatment suspended (until the toxicity resolves to either baseline or at least Grade 1) and the dose of abemaciclib must be reduced as outlined in Table JPBX.9.3.

If a patient experiences Grade 2 diarrhea that does not resolve with maximal supportive measures (refer to Section 9.6.2.2) within 24 hours to at least Grade 1, the study drug must be suspended (until the toxicity resolves to at least Grade 1) but abemaciclib dose reduction is not required. However, if a patient experiences persistent or recurrent Grade 2 diarrhea that does not resolve with maximal supportive measures (refer to Section 9.6.2.2) within 24 hours to at least Grade 1, then abemaciclib must be suspended (until the toxicity resolves to at least Grade 1) and the dose of abemaciclib must be reduced as outlined in Table JPBX.9.3.

9.4.2.1.2.4.   Hepatic Toxicity

Dose modifications and management for increased ALT are provided in Table JPBX.9.2. For persistent or recurrent Grade 2 ALT increased that does not resolve with maximal supportive measures within 7 days to baseline or Grade 1, or Grade 3 ALT increased, abemaciclib must be suspended until the toxicity has resolved to at least Grade 1 and the dose must be reduced by 1 dose level. Discontinue abemaciclib for Grade 3 increased ALT (>5.0 x ULN) with total bilirubin (TBL) >2 x ULN, in the absence of cholestasis. For Grade 4 ALT increased, the patient must be discontinued from abemaciclib. Refer to Section 10.3.3.1 for additional hepatic monitoring guidance.

9.4.2.1.2.5.   Interstitial Lung Disease/Pneumonitis

Dose modifications and management for ILD/pneumonitis are provided in Table JPBX.9.2. For persistent or recurrent Grade 2 ILD/pneumonitis that does not resolve with maximal supportive measures within 7 days to baseline or Grade 1, treatment with abemaciclib must be suspended until the toxicity resolves to baseline or Grade 1 and the dose must be reduced by 1 dose level. For Grade 3 or 4 ILD/pneumonitis, the patient must be discontinued from abemaciclib. Refer to Section 10.3.3.4 for additional ILD/pneumonitis monitoring guidance.

9.4.2.1.3.   Docetaxel

Investigators should consult the manufacturer's instructions for docetaxel for complete prescribing information (including warnings, precautions, contraindications, and adverse reactions) and follow institutional procedures for the administration of docetaxel. All implemented dose modifications are permanent. The doses must be modified according to the lowest hematology values and the highest degree of nonhematologic toxicities observed at any time during the previous cycle. If a patient develops several different toxic effects and there are conflicting recommendations, the dose reduction required for the clinically most severe toxic effect must be chosen.

Patients in Korea and Taiwan who receive 60 mg/m^2 dose of docetaxel who experience described toxicities should have treatment withheld until resolution of the toxicity and then resumed at 50 mg/m^2. For patients in Korea or Taiwan who were initially dosed at 60 mg/m^2 followed by

dose reduction to 50 mg/m^2, no further dose reduction will occur, and docetaxel treatment will be discontinued. Patients who develop ≥Grade 3 peripheral neuropathy should have docetaxel treatment discontinued entirely. Any Grade 3 or 4 nausea and vomiting should lead to an adaptation in the antiemetic therapy and docetaxel dosing should continue at an unchanged dosage. If this approach is not successful, docetaxel should be reduced.

9.4.2.1.3.1. Docetaxel Hypersensitivity Reactions

Patients should be observed closely for hypersensitivity reactions, especially during the first and second infusions. Severe hypersensitivity reactions characterized by generalized rash/erythema, hypotension and/or bronchospasm, or very rarely fatal anaphylaxis have been reported in patients premedicated with 3 days of corticosteroids. Severe hypersensitivity reactions require immediate discontinuation of the docetaxel infusion and aggressive therapy. Patients with a history of severe hypersensitivity reactions should not be rechallenged with docetaxel.

Hypersensitivity reactions may occur within a few minutes following initiation of a docetaxel infusion. If minor reactions such as flushing or localized skin reactions occur, interruption of therapy is not required. All patients should be premedicated with corticosteroids prior to the initiation of the infusion of docetaxel (see Section 9.6.1).

For mild symptoms: Complete docetaxel infusion. Supervise at bedside. No treatment required.

For moderate symptoms: Stop docetaxel infusion. Administer diphenhydramine 25 to 50 mg IV and dexamethasone 10 mg IV. Resume the docetaxel infusion after recovery of symptoms. If symptoms recur, stop the docetaxel infusion and remove patient from docetaxel treatment.

For severe life-threatening symptoms: Stop docetaxel infusion. Give IV diphenhydramine and dexamethasone as above. Add epinephrine or bronchodilators if indicated. The patient should be removed from docetaxel treatment.

Management of subsequent treatment cycles: The recommended pretreatment for subsequent infusions is 50 mg diphenhydramine IV and 10 mg dexamethasone IV 30 minutes prior to docetaxel infusion. This is in addition to the prescribed oral dexamethasone.

Patients with hypersensitivity reactions to docetaxel are at risk for recurrent reactions. For patients who experience moderate hypersensitivity reactions, the docetaxel should be administered over 2 hours for subsequent treatment courses in addition to premedication as noted above. These patients must be informed of the potential risk of recurrent allergic reactions and must be carefully monitored.

In cases of late-occurring (for example, appearance within 1 week after treatment) hypersensitivity symptoms of a localized or generalized pruritus, symptomatic treatment may be given (for example, oral antihistamine). Additional oral or IV premedication with antihistamine may also be given for the next cycle of treatment depending on the intensity of the reaction observed. No dose reductions will be made in any case.

9.4.2.1.3.2.   Docetaxel Hematologic Toxicity

Neutropenia (<2000 neutrophils/mm3) occurs in almost all patients treated with docetaxel 60 to 100 mg/m^2 and Grade 4 neutropenia (<500 cells/mm3) occurs in 85% of patients given 100 mg/m^2 and 75% of patients given 60 mg/m^2. Frequent monitoring of blood counts is therefore essential so that the dose can be adjusted. Docetaxel should not be administered to patients with neutrophils <1500 cells/mm^3.

9.4.2.1.3.3.   Docetaxel Fluid Retention

Severe fluid retention has been reported following docetaxel therapy. It is characterized by poorly tolerated peripheral edema, generalized edema, pleural effusion requiring urgent drainage, dyspnea at rest, cardiac tamponade, and pronounced abdominal distention (due to ascites). Patients should be premedicated with corticosteroids prior to each docetaxel administration to reduce the incidence and severity of fluid retention (see Section 9.6.1). When fluid retention occurs, peripheral edema usually starts in the lower extremities and may become generalized with a median weight gain of 2 kg. Patients with preexisting pleural effusions should be closely monitored from the first dose of docetaxel for the possible exacerbation of the effusion.

9.4.2.1.3.4.   Docetaxel Cutaneous Reaction

Localized erythema of the extremities with edema followed by desquamation has been observed. In case of severe skin toxicity, an adjustment in docetaxel dosage is recommended.

9.5.   Blinding

This is an open-label study.

See Section 12.1 for further details.

9.6.   Concomitant Therapy

Appropriate documentation of all forms of premedications, supportive care, and concomitant medications must be captured at each visit in the CRF. Concomitant medications and supportive care therapies must also be documented at the time of discontinuation and at the 30-day short-term follow-up visit.

Abemaciclib is extensively metabolized through oxidation by cytochrome P450 (CYP) 3A. In clinical drug interaction studies, coadministration of clarithromycin, a strong CYP3A inhibitor, increased exposure (area under the concentration-time curve) to abemaciclib by 3.4-fold (Study I3Y-MC-JPBE) and coadministration of rifampin, a strong CYP3A inducer, decreased exposure to abemaciclib by 95% (Study I3Y-MC-JPBF). Therefore, grapefruit or grapefruit juice as well as inducers and inhibitors of CYP3A should be substituted or avoided if possible (Attachment 10). Although dexamethasone is a CYP3A4 inducer, use during the study is allowed. The dose of corticosteroids, including dexamethasone, will be captured throughout the study.

Abemaciclib can be coadministered with drugs that are substrates of CYP enzymes.

Abemaciclib and/or its major metabolites inhibit the efflux transporters P-glycoprotein and breast cancer resistance protein and renal transporters organic cation transporter 2, MATE1, and MATE2-K at clinically relevant concentrations. Therefore, substrates of these transporters such

as metformin and those with a narrow therapeutic index such as digoxin and dofetilide should be substituted or avoided if possible.

Docetaxel is a CYP3A4 substrate. Grapefruit juice as well as inducers and strong inhibitors of CYP3A4 should be substituted or avoided if possible (Attachment 10). If systemic administration of a CYP3A4 inhibitor cannot be avoided in patients receiving treatment with docetaxel injection, consider close monitoring for toxicity and/or docetaxel injection dose reduction. The dose of corticosteroids, including dexamethasone, will be captured throughout the study.

Dexamethasone is a known CYP3A4 inducer. Patients receiving docetaxel should be pretreated with dexamethasone per label recommendations. All patients may receive supportive therapy with dexamethasone, preferably ≤10 days, if clinically indicated. Patients requiring more than 10 days of dexamethasone therapy will not incur a protocol deviation.

With the exceptions listed in the sections below, no other chemotherapy, experimental medications, other anticancer therapy, immunotherapy, hormonal cancer therapy, radiation, surgery for cancer, or experimental medications will be permitted while patients are on study treatment.

9.6.1. Premedication Prior to Infusion of Docetaxel

Investigators should consult the manufacturer's instructions for docetaxel for complete prescribing information (including warnings, precautions, contraindications, and adverse reactions) and follow institutional procedures for the administration of docetaxel. Patients should be premedicated with corticosteroids, such as dexamethasone 16 mg per day (for example, 8 mg twice a day) for 3 days starting 1 day prior to docetaxel administration in order to reduce the incidence and severity of fluid retention, as well as the severity of hypersensitivity reactions. Additional antiemetic premedication may be employed at the discretion of the investigator. All premedication administered must be adequately documented in the electronic CRF (eCRF).

9.6.2. Supportive Care

Patients will receive supportive care as judged by their treating physician, if necessary. Supportive care measures may include but are not limited to antidiarrheal agents, antiemetic agents, opiate and nonopiate analgesic agents, appetite stimulants, and granulocyte and erythroid growth factors. Details of interventions (for example, medications such as sedatives, antibiotics, analgesics, antihistamines, steroids, or erythroid-stimulating agents), procedures (for example, paracentesis or thoracentesis), or blood products (for example, blood cells, platelets, or fresh frozen plasma transfusions) should be recorded on the eCRFs. If it is unclear whether a therapy should be regarded as supportive care, the investigator should consult the Lilly CRP. Use of any supportive care therapy should be reported on the eCRFs. Guidelines regarding the use of other specific supportive care agents are presented below.

9.6.2.1. Palliative Radiotherapy

Palliative radiotherapy, unless required due to progressive disease, is permitted during the study.

9.6.2.2. Supportive Management for Diarrhea

At randomization, patient should receive instructions on the management of diarrhea. In the event of diarrhea (see Attachment 11), supportive measures should be initiated <u>as early as possible</u>. These include the following:

- At the first sign of loose stools, the patient should initiate anti-diarrheal therapy (for example, loperamide) and notify the investigator/site for further instructions and appropriate follow-up.
- Patients should also be encouraged to drink fluids (for example, 8 to 10 glasses of clear liquids per day).
- Site personnel should assess response within 24 hours.
- If diarrhea does not resolve with anti-diarrheal therapy within 24 hours to either baseline or Grade 1, study drug should be suspended until diarrhea is resolved to baseline or Grade 1.
- When study drug recommences dosing should be adjusted as outlined in Sections 9.4.2.1.1, 9.4.2.1.2, and 9.4.2.1.3.

In severe cases of diarrhea, the measuring of neutrophil counts and body temperature and proactive management of diarrhea with antidiarrheal agents should be considered.

If diarrhea is severe (requiring IV rehydration) and/or associated with fever or severe neutropenia, broad-spectrum antibiotics such as fluoroquinolones must be prescribed.

Patients with severe diarrhea or any grade of diarrhea associated with severe nausea or vomiting should be carefully monitored and given intravenous fluid (IV hydration) and electrolyte replacement.

9.6.2.3. Granulocyte-Colony Stimulating Factors

The use of granulocyte-colony stimulating factor (G-CSF) is permitted during investigational therapy at the discretion of the investigator. G-CSF or similar agents are strongly recommended following Grade 3 or 4 neutropenia of duration >5 days or following any incidence of febrile neutropenia (ANC <1.0 x 10^3/μL [1.0 x 10^9/L] with a single temperature $\geq$38.3°C or a sustained temperature of $\geq$38.0°C for >1 hour).

9.6.2.4. Therapy for Febrile Neutropenia

Patients experiencing febrile neutropenia, especially with diarrhea or dyspnea, should be managed in a hospital setting according to standard procedures, with the urgent initiation of IV antibiotic therapy. Events that require a patient to be hospitalized are considered SAEs (see Section 10.3.1.1).

9.6.2.5. Bisphosphonates and RANK-L Targeted Agents

Use of bisphosphonates or approved receptor activator of nuclear factor kappa-B ligand (RANK-L) targeted agents (for example, denosumab) is permitted during participation in the

study. Patients should if possible begin treatment with bisphosphonates or RANK-L targeted agents at least 7 days prior to randomization. Patients who start the study receiving bisphosphonates or RANK-L targeted agents should, if possible, avoid switching treatments (for example, replacing a bisphosphonate with denosumab) while on study treatment. However, patients switching treatments will not incur a protocol deviation. Patients are not permitted to begin treatment with bisphosphonates or RANK-L targeted agents while receiving study treatment. After study treatment discontinuation, use of bisphosphonates or RANK-L targeted agents is at the discretion of the treating physician.

9.6.2.6. Other Study Conditions: Surgery (or Equally Considered Procedure) During Study Treatment Phase

If any surgery should be required during the study (palliative surgery or medically indicated by the investigator), the patient should undergo radiologic evaluation before surgery for documentation of disease status. Elective, nonemergent surgery is strongly discouraged during study participation. The time of study treatment interruption before surgery should be at least 7 days following the last dose of study treatment. Patients may resume all study treatment no less than 28 days following surgery, provided there has been adequate recovery in the opinion of the investigator. Following surgery, radiological evaluation of disease is required prior to resumption of study treatment. The duration of treatment suspension for surgical procedure and healing is not considered noncompliance and will not incur a protocol violation.

9.6.2.7. Antiemetic Agents

The use of antiemetic agents is permitted during this study and at the discretion of the investigator. However, it is recommended to follow the guidelines of the Multinational Association of Supportive Care in Cancer and American Society of Clinical Oncology; dexamethasone may be sufficient, but 5-HT3 antagonists and NK1 antagonists may be used (Kris et al. 2006; Gralla et al. 2010).

9.6.2.8. Analgesic Agents

The use of analgesic agents is permitted at the discretion of the investigator.

9.6.2.9. Appetite Stimulants

The use of appetite stimulants is permitted at the discretion of the investigator. Acceptable agents include, but are not limited to, megestrol acetate and dronabinol.

9.7.   Treatment Compliance

Patient compliance with study drug will be assessed at each visit.

Abemaciclib compliance will be assessed by counting returned solid oral dosage units. Study medication administration data will be recorded in the patient's medical record and eCRF.

Patients who are significantly noncompliant will be discontinued from the study. A patient will be considered significantly noncompliant if he or she misses more than 7 or more consecutive days of abemaciclib (full doses), or more than 25% cumulative days of abemaciclib (full doses) during the study. Similarly, a patient will be considered significantly noncompliant if he or she is judged by the investigator to have intentionally or repeatedly taken more than the prescribed

amount of medication. Abemaciclib dose suspensions or delays related to at toxicity may occur and will not result in a patient being considered as noncompliant.

Docetaxel will be administered only by trained medical personnel at the investigational sites and under the direction of the investigator. As a result, monitoring of patient compliance is ensured. Patients who require a delay of more than 14 days in starting a new cycle of docetaxel (> 35-day interval between consecutive cycles) should be removed from treatment.

9.8. Patient Diaries

The study will include patient diaries to provide dosing instructions, help patients with treatment planning, and track actual doses of study abemaciclib taken by the patient. Information from the diaries may be used for documenting study treatment compliance as well as dosing time relative to PK blood draws and electrocardiogram (ECG) collection.

10.   Efficacy, Health Outcome/Quality of Life Measures, Safety Evaluations, Sample Collection and Testing, and Appropriateness of Measurements

Written informed consent must be obtained prior to any study-specific pretreatment evaluations.

Study procedures related to efficacy, safety, health outcome/quality of life measures, sample collection, and testing assessments and their timing are described in the sections below and shown in the Study Schedule (Attachment 1).

10.1. Efficacy Measures

10.1.1. Efficacy Assessments at Baseline and during Study Treatment

Within 28 days before the first dose of study drug, baseline tumor measurements will be performed on each patient. Computed tomography (CT), including spiral CT, scans and MRI are the preferred methods of measurement. Tumor assessments should include the chest and abdominal region.

The CT portion of a positron emission tomography (PET)-CT scan may be used as a method of response assessment if the site can document that the CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast). A PET scan alone or as part of a PET-CT may be performed for additional analyses but cannot be used to assess response according to RECIST.

The method of assessment used at baseline must be used consistently for tumor assessment and will be repeated every other cycle, beginning with Cycle 3 Day 1 ($\pm$3 days). If possible, the patient should have postbaseline assessments completed before Day 1 of the required cycles for reassessments to permit results to be discussed with the patient at the day of the patient visit to the clinic. If a cycle is delayed, tumor assessment should be concurrent with Day 1 of the new cycle.

For patients continuing treatment after study completion (that is, during the continued access period), efficacy assessments (frequency and type of assessments) will be at the discretion of the investigator, based on the standard of care.

10.1.2. Efficacy Assessments during the Study Period Postdiscontinuation Follow-Up

Postdiscontinuation follow-up during the study period will be conducted as described in the Study Schedule (Attachment 1).

For those patients who discontinue study treatment without objectively measured PD, the investigative sites will continue to monitor patients and periodically evaluate tumor response every 6 weeks by the same method used at baseline and throughout the study until the patient has objective disease progression, or study completion. After the patient has objective disease

progression, radiologic tests are no longer required and the patient will be followed up approximately every 60 days (±14 days) until the patient's death or overall study completion.

Response (CR or PR) should be confirmed before the initiation of additional anticancer therapy. However, initiation of new therapy should not be delayed solely to confirm response.

Efficacy assessments (frequency and type of assessments) for patients still on treatment during the continued access period will be at the discretion of the investigator, based on the standard of care.

Lilly will continue to collect survival data on all patients but may reduce data collection for other efficacy data. Lilly will notify investigators when this reduced data collection can begin.

10.1.3. Primary Efficacy Measure

The primary efficacy measure is investigator-assessed PFS as defined as the time from randomization until the first evidence of objective progression as defined by RECIST 1.1 (Eisenhauer et al. 2009) or death from any cause, whichever is earlier. Patients who have neither progressed nor died will be censored at the day of their last radiographic tumor assessment, if available, or the date of randomization if no postbaseline radiographic assessment is available. The detailed censoring rules are described in Table JPBX.10.1.

The primary PFS analysis will be derived from the local investigator's tumor assessments.

Lilly or its designee will collect and store all tumor measurement images on all enrolled patients throughout the study. An central review of imaging scans will be performed by Lilly or its designee.

10.1.4. Secondary Efficacy Measures

The following secondary efficacy measures (Table JPBX.10.1) will be collected at the times shown in the Study Schedule (Attachment 1).

Table JPBX.10.1.   Secondary Efficacy Endpoints

Endpoint	Definition
Overall Survival	The time from the date of study enrollment to the date of death from any cause
Overall Response Rate	The proportion of patients with CR or PR according to RECIST v1.1
Disease Control Rate	The proportion of patients with CR, PR, or SD according to RECIST v1.1
Time to Worsening ECOG Performance Status (PS)	The time from the date of randomization to the date of first PS ≥ 2

Abbreviations: CR = complete response; PR = partial response; PS = performance status; RECIST = Response Evaluation Criteria In Solid Tumors; SD = stable disease.

Overall Survival (OS): OS duration is measured from the date of randomization of any study drug to the date of death from any cause. For each patient who is not known to have died as of

the data-inclusion cutoff date for a particular analysis, OS will be censored for that analysis at the date of last contact prior to the data inclusion cutoff date (contacts considered in the determination of last contact date include AE date, lesion assessment date, visit date, and last known alive date).

Overall Response Rate: The overall response rate is the percentage of patients with a best response of CR or PR.

Disease Control Rate (DCR): The DCR is the percentage of patients with a best response of CR, PR, or SD.

Time to Worsening ECOG Performance Status: will be defined as the time from randomization to an ECOG PS evaluation of 2 or worse. Patients with no evaluation of 2 or worse will have their time to deterioration of PS censored at the date of the last PS evaluation.

10.1.5. Exploratory Efficacy Measures

Biomarkers: Exploratory analysis using blood and tumor tissues will be done to explore potential biomarkers related to the mechanism of action of abemaciclib, docetaxel, the cell cycle, and/or the pathogenesis of lung cancer to better understand relationships of cellular signaling defects, exposure, and response with clinical outcomes.

Change in Tumor Size: Change in tumor size will be measured using target lesion measurements. This measurement will only be available on patients with measurable disease.

10.2. Health Outcome/Quality of Life Measures

10.2.1. Patient-Reported Outcomes

Patient-reported outcomes will be measured using 2 standardized questionnaires, the MDASI-LC and the EQ-5D-5L. The MDASI-LC questionnaire is a well-developed and validated assessment with adequate measurement properties to capture well-known cancer disease- and treatment-related symptoms and the consequences of these patient experiences. Inclusion of this MDASI-LC is intended to establish the measurement properties of this questionnaire in this setting.

Items of particular interest are the patient-rated diarrhea and fatigue; it will be important to estimate the effects of these symptoms on the 6 MDASI Interference Items as well as on the EQ-5D-5L quality of life measures (that is, the health state utility index and the visual analog rating of health status). Additionally, the inclusion of 8 additional MDASI-LC items to evaluate patient-reported effects of brain metastases as well as 3 additional MDASI-LC exploratory items will be evaluated for redundancy and validity. This development work will help to inform the patient-reported consequences of treatment and will provide important information to distinguish the relative benefits of the evaluated treatments. Importantly, establishing the validity and conceptual framework for this MDASI-LC and EQ-5D-5L set of items will allow us to prespecify important constructs in future clinical trials.

Patient-reported questionnaires should be completed by all patients except when there is no available translation for a language in which the patient is fluent or literate.

At each time points identified in the Study Schedule (Attachment 1), a paper copy of the questionnaire should be administered to the patient prior to extensive interaction with the site staff and study drug administration.

On each measurement occasion and as specified in the Study Schedule (Attachment 1) (that is, once during screening, on Day 1 of each cycle, and at the Visit 801 follow-up visit), the patients should first complete the MDASI-LC questionnaire. Only after the MDASI-LC is completed should the patient complete the EQ-5D-5L questionnaire.

10.2.1.1. MDASI-LC

The MDASI-LC (Mendoza et al. 2011) is a 22-item questionnaire that includes 13 core symptom items, 6 core interference items, and 3 lung-specific symptom items (coughing, constipation, and sore throat). An additional MDASI page will include 11 exploratory items that are not a standard part of the validated MDASI-LC questionnaire. Advanced lung cancer is a leading source of brain metastases, and symptoms related to brain metastases are described by 8 of these exploratory items (weakness on 1 side of body, difficulty understanding, difficulty speaking, seizures, difficulty concentrating, vision, change in appearance, and irritability). These 8 exploratory items are sourced from the brain-specific items included in the validated MDASI-Brain Tumor questionnaire. The remaining 3 exploratory items comprise one additional item to further evaluate brain symptoms (headache) and 2 items to evaluate expected treatment-related toxicities including diarrhea and changes to the skin (that is, skin changes or skin rash).

"Worst pain" in the past 24 hours (MDASI-LC Item 1) and changes in the use of pain medication since the last assessment (that is, previous clinic visit) will be separately and jointly assessed as described in Section 12.2.10.1.

Responses for the MDASI-LC items are captured through the use of 11-point numeric rating scales anchored at 0 (*not present* or *does not interfere*) and ranged through 10 (*as bad as you can imagine* or *completely interferes*). The MDASI-LC recall period is 24 hours, and typical completion time for this instrument is less than 5 to 10 minutes.

10.2.1.2. EQ-5D-5L

The EuroQol 5 Dimension 5 Level (EQ-5D-5L) is a self-reported standardized and validated measure of health status, and will allow for comparison with other tumor types and disease states (Janssen et al. 2008). Responses to the EQ-5D-5L descriptive items (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) constitute a patient's profile that is converted to a single summary index by applying a formula that essentially attaches population-specific weights to each 5-dimension response pattern. These index scores represent utilities that are applied to survival outcomes as a QoL adjustment important in conducting economic evaluations of comparative treatment benefit. Additionally, the EQ-5D-5L also includes a visual analog scale (VAS or "thermometer") used to assess patients' current health state through use of a 0-100

continuous "thermometer" rating scale.

The EQ-5D-5L is designed to be used in conjunction with other patient-reported measures. Patients will complete the questionnaire at each specified visit and according to the Study Schedule (Attachment 1).

Administration is preferably scheduled after the MDASI-LC, and before extensive contact with study personnel or clinicians, which could result in biased patient response. The recall period is "today." The EQ-5D-5L is designed for respondent self-completion within a period of only a few minutes.

10.2.2. Resource Utilization

Investigators will be asked to report the use of **all** concomitant medications (in particular, analgesics, bisphosphonates, and RANK-L targeted agents), blood product transfusions, radiation therapy, surgery, and hospitalization days.

Data on each individual prescription and over-the-counter analgesic medication will be recorded on the Concomitant Medication eCRF. The use of pain medications from the previous visit should be reviewed with the patient at each subsequent visit. Any changes to analgesic use based on this information should be recorded on the Concomitant Medication eCRF, and the term "any changes" includes new or stopped analgesics. Data on neurosurgical blocks will be recorded on the eCRF. This information should be collected during the study and at the 30-day follow-up visit. Changes in pain medication will be evaluate separately and in conjunction with changes in the level of self-reported MDASI-LC pain assessments to avoid confounding of study drug treatment effect with the analgesic effect of increased or decreased intensity of pain/analgesic medication use.

10.3. Safety Evaluations

Investigators are responsible for monitoring the safety of patients who have entered this study and for alerting Lilly or its designee to any event that seems unusual, even if this event may be considered an unanticipated benefit to the patient.

The investigator is responsible for the appropriate medical care of patients during the study.

The investigator remains responsible for following, through an appropriate health care option, AEs that are serious, considered related to the study, or that caused the patient to discontinue before completing the study. The patient should be followed until the event is resolved or explained. Frequency of follow-up evaluation is left to the discretion of the investigator.

The timing of all safety evaluations is shown in the Study Schedule (Attachment 1). Table JPBX.10.2 presents a summary of AE and SAE reporting guidelines. Table JPBX.10.2 also shows which database or system is used to store AE and SAE data.

Table JPBX.10.2.   Adverse Event and Serious Adverse Event Reporting Guidelines

Period	Types of AEs/SAEs to be Reported	Collection Database	Lilly Safety System
Baseline (pretreatment)	Preexisting conditions	x	
	All AEs	x	
	SAEs related to protocol procedures	x	x
Study treatment period	All AEs	x	
	All SAEs	x	x
30-day short-term postdiscontinuation follow-up	All AEs	x	
	All SAEs	x	x
Long-term postdiscontinuation follow-up	All SAEs related to protocol procedures or study drug	x	x
Continued access period	All AEs	x	
	All SAEs	x	x
Continued access follow-up	All AEs	x	
	All SAEs	x	x
After the patient is no longer participating in the study (that is, no longer receiving study treatment and no longer in follow-up)	All SAEs related to protocol procedures or study drug that the investigator becomes aware of		x

Abbreviations: AE = adverse event; SAE = serious adverse event.

10.3.1. Adverse Events

Lilly has standards for reporting AEs that are to be followed regardless of applicable regulatory requirements that may be less stringent. A clinical study AE is any untoward medical event associated with the use of a drug in humans, whether or not it is considered related to that drug.

Lack of drug effect is not an AE in clinical trials, because the purpose of the clinical trial is to establish drug effect.

Any clinically significant findings from electrocardiograms (ECG; for example, QTc prolongation), labs, vital sign measurements, other procedures, and so on that result in a diagnosis should be reported to Lilly or its designee. All non-clinically significant findings must be documented in the patient record as not clinically significant and therefore will not be documented in the eCRF.

Cases of pregnancy that occur during maternal or paternal exposures to study drug should be reported. Data on fetal outcome and breast-feeding are collected for regulatory reporting and drug safety evaluation.

Study site personnel will record the occurrence and nature of each patient's preexisting conditions, including clinically significant signs and symptoms of the disease under treatment in the study.

After the ICF is signed, site personnel will record the occurrence and nature of any AEs and any change in the preexisting condition(s). All AEs related to protocol procedures are reported to Lilly or its designee.

In addition, the investigator will record all relevant AE/SAE information in the CRF. Investigators will be instructed to report to Lilly or its designee their assessment of the potential relatedness of each AE to protocol procedure or study drug via eCRF.

The investigator will decide whether he or she interprets the observed AEs as related to disease, to the study medication, study procedure, or other concomitant treatment or pathologies. To assess the relationship of the AE to study drug or study procedure, the following terminologies are defined:

- **Probably related**: a direct cause and effect relationship between the study treatment and the AE is likely
- **Possibly related**: a cause and effect relationship between the study treatment and the AE has not been demonstrated at this time and is not probable, but is also not impossible
- **Does not know:** the investigator cannot determine
- **Not related**: without question, the AE is definitely not associated with the study treatment

The investigator should classify all "probably related," "possibly related," or "does not know" AEs and SAEs as related to study drug/study procedure.

Patients will be evaluated for AEs at each visit and will be instructed to call their physician to report any AEs between visits.

The National Cancer Institute (NCI)-CTCAE v 4.0 will serve as the reference document for choosing appropriate terminology for, and grading the severity of, all AEs and other symptoms. For AEs without matching terminology within the NCI-CTCAE v 4.0 criteria, the investigator will be responsible for selecting the appropriate system organ class and assessing severity grade based on the intensity of the event.

In addition to collecting the AE verbatim and the CTCAE severity grade, AE verbatim text will also be mapped by Lilly or its designee to corresponding terminology within the Medical Dictionary for Regulatory Activities (MedDRA) dictionary.

If a patient's dosage is reduced or treatment is discontinued as a result of an AE, study site personnel must clearly report to Lilly or its designee via eCRF the circumstances and data leading to any such dosage reduction or discontinuation of treatment.

10.3.1.1. Serious Adverse Events

An SAE is any adverse event from this study that results in one of the following outcomes:

- death
- a life-threatening experience (that is, immediate risk of dying)
- persistent or significant disability/incapacity
- initial or prolonged inpatient hospitalization
- congenital anomaly/birth defect
- considered significant by the investigator for any other reason

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious adverse drug events when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Serious adverse event collection begins after the patient has signed informed consent and has received study drug. If a patient experiences an SAE after signing informed consent, but prior to receiving study drug, the event will not be reported as serious unless the investigator feels the event may have been caused by a protocol procedure.

Data on SAEs that occur before the end of trial will be stored in the collection database and the Lilly Safety System.

Study site personnel must alert Lilly or its designee of any **serious** adverse event (SAE) within 24 hours of investigator awareness of the event via a sponsor-approved method. If study site personnel contact Lilly or its designee by telephone regarding an SAE, study site personnel must also immediately provide official notification on study-specific SAE forms.

This 24-hour notification requirement refers to the initial SAE information and all follow-up SAE information.

Planned surgeries should not be reported as SAEs unless the underlying medical condition has worsened during the course of the study.

Planned hospitalizations or procedures for preexisting conditions that are already recorded in the patient's medical history at the time of study enrollment should not be considered SAEs. Hospitalization or prolongation of hospitalization without a precipitating clinical AE (for example, for the administration of study treatment or other protocol-required procedure) should not be considered SAEs.

Serious adverse events due to disease progression, including death, should not be reported unless the investigator deems them to be possibly related to the study drug.

If an investigator becomes aware of an SAE occurring after the patient's participation in the trial has ended, and the investigator believes that the SAE is related to a protocol procedure or study drug, the investigator should report the SAE to the sponsor, and the SAE will be entered in the Lilly Safety System.

Information on SAEs expected in the study population independent of drug exposure and that will be assessed by the sponsor in aggregate periodically during the course of the trial may be found in the IB.

10.3.1.2. Suspected Unexpected Serious Adverse Reactions

Suspected unexpected serious adverse reactions (SUSARs) are serious events that are not listed in the Development Core Safety Information in the IB and that the investigator identifies as related to the study drug or study procedure. United States 21 CFR 312.32 and European Union Clinical Trial Directive 2001/20/EC and the associated detailed guidances or national regulatory requirements in participating countries require the reporting of SUSARs. Lilly has procedures that will be followed for the recording and expedited reporting of SUSARs that are consistent with global regulations and associated detailed guidances.

10.3.2. Other Safety Measures

10.3.2.1. Electrocardiograms

For each patient assigned to abemaciclib, a single local 12-lead digital ECGs will be collected according to the Study Schedule (Attachment 1 and Attachment 8). Patients must be supine (or reclined as flat as possible) for approximately 5 to 10 minutes before ECG collection and remain supine but awake during ECG collection.

Electrocardiograms may be obtained at additional times, when deemed clinically necessary. Collection of more ECGs than expected at a particular time point is allowed when needed to ensure high-quality records.

Electrocardiograms will be interpreted by a qualified physician (the investigator or qualified designee) at the site as soon after the time of ECG collection as possible, and ideally while the patient is still present, to determine whether the patient meets entry criteria and for immediate patient management, should any clinically relevant findings be identified.

After enrollment, if a clinically significant increase in the QT/QTc interval from baseline, or other clinically significant quantitative or qualitative change from baseline, is present, the investigator will assess the patient for symptoms (for example, palpitations, near syncope, syncope) and to determine if the patient can continue in the study. The investigator or qualified designee is responsible for determining if any change in patient management is needed and must document his/her review of the ECG printed at the time of evaluation.

10.3.3. Safety Monitoring

The Lilly CRP will monitor safety data throughout the course of the study.

Lilly will review SAEs within time frames mandated by company procedures. The Lilly CRP will, as is appropriate, consult with the functionally independent Global Patient Safety therapeutic area physician or clinical scientist, and review:

- trends in safety data
- laboratory analytes
- adverse events

10.3.3.1. Special Hepatic Safety Data Collection

If a study patient experiences elevated ALT ≥5×ULN and elevated total bilirubin (TBL) ≥2×ULN, or ALT >8x ULN for patients with underlying baseline hepatic metastases, liver tests (Attachment 3), including ALT, AST, TBL, direct bilirubin, gamma glutamyl transferase (GGT), and creatine phosphokinase (CPK), should be repeated within 3 to 5 days to confirm the abnormality and to determine if it is increasing or decreasing. If the abnormality persists or worsens, clinical and laboratory monitoring should be initiated by the investigator, based on the hepatic monitoring tests (Attachment 3) and in consultation with the Lilly CRP. Monitoring of ALT, AST, and TBL should continue until levels normalize or return to approximate baseline levels. Additional diagnostic testing should be considered to rule out cause of increased liver enzymes per the investigator's discretion.

Hepatic monitoring tests (Attachment 3) should be collected in the event that 1 or more of the following conditions is met for the patient during the course of the study:

- ALT ≥5×ULN and TBL ≥2×ULN

- ALT >8x ULN for patients with underlying hepatic metastasis

- discontinuation from study treatment due to a hepatic event or an abnormality of liver tests

10.3.3.2. Renal Function

Abemaciclib has been shown to increase serum creatinine due to inhibition of renal tubular secretion of creatinine without affecting cystatin C-calculated glomerular filtration rate. Increases in serum creatinine occurred within the first 2 weeks of treatment, remained stable through the treatment period, and were reversible upon treatment discontinuation. If deterioration of renal function is suspected, serum creatinine should not be the only measure used to assess a patient's renal function.

Dose adjustment (omission, reduction, or discontinuation) should not solely be based on interpretation of serum creatinine values because these may not reflect renal function. If deterioration of renal function is suspected per the investigator's clinical assessment, dose alteration should follow the protocol guidance for non-hematological toxicities (Table JPBX.9.3).

10.3.3.3. Venous Thromboembolic Events (VTEs)

In the randomized Phase 3 studies in breast cancer patients who received abemaciclib in combination with endocrine therapy, there was a greater number of patients who experienced VTEs in the abemaciclib plus endocrine therapy arm than in the placebo plus endocrine therapy arm. The majority of the events were non-serious and were treated with low-molecular-weight heparin. Generally, these events did not result in discontinuation of the study treatment. At this time, the mechanism underlying the association between abemaciclib and the occurrence of VTEs is not known. For suspected or confirmed VTE (e.g., deep vein thrombosis or pulmonary embolism), treatment should occur according to usual clinical practice. In studies with single-agent abemaciclib use in the mBC population or other tumor types, including NSCLC, no increased rates of VTEs were observed as compared to the incidence of VTEs for these particular patient populations who were treated with other anticancer agents.

10.3.3.4. Interstitial Lung Disease/Pneumonitis

Interstitial lung disease/pneumonitis has been identified as an adverse drug reaction for abemaciclib. The majority of events observed in clinical trials were Grade 1 or Grade 2 with serious cases and fatal events reported. Additional information is available in the IB.

Ask your patients to report any new or worsening pulmonary symptoms such as dyspnea, cough, and fever, and investigate and treat as per your local clinical practice (including corticosteroids as appropriate). If ILD/pneumonitis is suspected, investigations may include imaging, such as high-resolution computed tomography, bronchoalveolar lavage, and biopsy as clinically indicated.

Refer to Table JPBX.9.2 for guidance on dose adjustments of abemaciclib for patients with ILD/pneumonitis (see Attachment 11 for ILD/pneumonitis CTCAE grades). Discontinue abemaciclib in cases of severe ILD/pneumonitis.

10.3.4. Complaint Handling

Lilly collects product complaints on study drugs used in clinical trials in order to ensure the safety of study participants, monitor quality, and to facilitate process and product improvements.

Complaints related comparator drugs or concomitant drugs are reported directly to the manufacturers of those drugs/devices in accordance with the package insert.

The investigator or his/her designee is responsible for handling the following aspects of the product complaint process in accordance with the instructions provided for this study:

- recording a complete description of the product complaint reported and any associated AEs using the study-specific complaint forms provided for this purpose
- faxing the completed product complaint form within 24 hours to Lilly or its designee

If the investigator is asked to return the product for investigation, he/she will return a copy of the product complaint form with the product.

10.4. Sample Collection and Testing

Attachment 1 lists the schedule for sample collections in this study.

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Attachment 2 lists the specific tests that will be performed for this study and whether these will be performed at a central or local laboratory.

Attachment 9 provides a summary of the estimated maximum number and volume of invasive samples, for all sampling, during the study.

10.4.1. Samples for Study Qualification and Health Monitoring

Blood samples will be collected to determine whether patients meet inclusion/exclusion criteria and to monitor patient health. Enrollment and treatment decisions may be based upon results of tests performed locally. If local laboratory tests are used for this purpose, then a duplicate specimen must be submitted to the central laboratory. Discrepancies between the local and central laboratory that may have an impact on eligibility or treatment decisions will not be considered protocol violations.

Investigators must document their review of each laboratory safety report.

Samples collected for specified laboratory tests will be destroyed within 60 days of receipt of confirmed test results. Tests are run and confirmed promptly whenever scientifically appropriate. When scientific circumstances warrant, however, it is acceptable to retain samples to batch the tests run, or to retain the samples until the end of the study to confirm that the results are valid. Certain samples may be retained for a longer period, if necessary, to comply with applicable laws, regulations, or laboratory certification standards.

10.4.2. Samples for Biomarkers

Samples for biomarker research to be collected from all patients in this study are the following:

- tumor tissue
- whole blood
- plasma

Analyses may include, but are not limited to, nucleic acid and protein profiles to better understand the disease process and to develop predictive biomarkers. These samples are described in the following sections.

10.4.2.1. Archived Tumor Tissue

For patients in the study, a small amount of preserved tumor tissue (either resected whole or partial tumor block, or core needle biopsy), previously taken to evaluate the patient's disease, is required to be provided by sites upon patient randomization for biomarker research. Re-biopsy after progression from prior therapy is not required.

Available FFPE primary and/or metastatic tumor tissue should be as a block or 10 to 15 unstained slides. However, if archived tissue is limited, a minimum of 10 slides should be submitted to meet the inclusion criteria of the study. Any block submitted will be returned to the site. Any slides will be discarded within 15 years after last patient visit for the trial, unless otherwise determined by government or local law.

In tumor tissue samples, the cell cycle pathway components and markers relevant to lung cancer pathogenesis may be evaluated to assess any potential correlation with response to abemaciclib and/or docetaxel. Tumor samples may be analyzed to explore potential tumor gene signature(s) associated with response or resistance to abemaciclib therapy. These studies may be analyzed at a laboratory designated by the sponsor and may include immunohistochemistry of proteins, copy number amplifications, RNA gene-expression profiling, and/or genetic analyses of the tumor specimen DNA. Such analyses may employ targeted or high-throughput sequencing approaches. For this purpose, the results of this analysis will be correlated with clinical efficacy data.

10.4.2.2. Whole Blood Samples for Pharmacogenetic Evaluations

There is growing evidence that genetic variation may impact a patient's response to therapy. Variable response to therapy may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion, the mechanism of action of the drug, the disease etiology, and/or the molecular subtype of the disease being treated. Therefore, where local regulations and ERBs allow, a whole blood sample will be collected for pharmacogenetic analysis.

Samples may be genotyped and analysis may be performed to evaluate a genetic association with response to abemaciclib. These investigations may be limited to a focused candidate gene study or, if appropriate, genome-wide analysis may be performed to identify regions of the genome associated with the variability observed in drug response. The pharmacogenetic biomarker samples will only be used for investigations related to disease and drug or class of drugs under study in the context of this clinical program. They will not be used for broad exploratory unspecified disease or population genetic analysis.

In the event of an unexpected AE or the observation of unusual response, the pharmacogenetic biomarker samples may be genotyped and analysis may be performed.

The samples will be coded with the patient number and stored for up to a maximum 15 years after the last patient visit for the study at a facility selected by the sponsor unless otherwise determined by government or local law.

The samples and any data generated from them can only be linked back to the patient by investigator site personnel. The duration allows the sponsor to respond to regulatory requests related to the study drug.

Samples will be destroyed according to a process consistent with local regulation.

10.4.2.3. Plasma Samples for Exploratory Biomarker Evaluations

Ethylenediamine tetraacetic acid (EDTA)-anticoagulated plasma samples will be collected and analysis may be performed on biomarkers that may play a role in the abemaciclib mechanism of action. The evaluation of these samples may involve analysis of DNA, RNA, and proteins (including any of these components derived from exosomes) to investigate their association with observed clinical outcomes to study drug. The samples will be coded with the patient number

and stored for up to a maximum 15 years. Details for collecting, processing, and storing the samples are similar those provided in Section 10.4.2.2.

10.4.3. Samples for Drug Concentration Measurements Pharmacokinetics - Abemaciclib Only

At the visits and times specified in the Pharmacokinetic and Pharmacodynamic Sampling Schedule (Attachment 8), venous blood samples of approximately 2 mL each will be collected to determine the plasma concentrations of abemaciclib and its major metabolites LSN2839567 and LSN3106726.

Instructions for the collection and handling of blood samples will be provided by the sponsor. It is preferred that the blood samples be obtained from a peripheral location. Blood samples will be allowed from central access devices but a sample drawn from a central catheter of any type for PK must take precautions to prevent obtaining a dilute sample. If multiple samples are obtained centrally, the PK sample should be the last specimen drawn to reduce the potential for a diluted or improperly drawn sample. The actual date and time (24-hour clock time) of each sampling will be recorded. In addition, the actual date and time of doses proximal to PK sampling days will be recorded on the appropriate form, according to the instructions provided.

A maximum of 5 samples may be drawn at additional time points during the study if warranted and agreed upon between both the investigator and Lilly.

These samples will be analyzed at a laboratory designated by the sponsor. Plasma concentrations of abemaciclib plus its metabolites LSN2839567and LSN3106726 will be assayed using a validated liquid chromatography-tandem mass spectrometry method.

Bioanalytical samples collected to measure investigational product concentration and metabolism and/or protein binding will be retained for a maximum of 1 year following last patient visit for the study. The PK samples will be stored at a facility designated by the sponsor.

10.5. Appropriateness of Measurements

Efficacy measurements by radiographic imaging are standard, widely used, generally recognized as reliable, accurate, and able to discriminate between effective and ineffective agents.

Safety measurements by laboratory monitoring are standard, widely used, generally recognized as reliable, accurate, and able to discriminate between agents with acceptable and unacceptable safety profiles.

11. Data Quality Assurance

To ensure accurate, complete, and reliable data, Lilly or its representatives will do the following:

- provide instructional material to the study sites, as appropriate
- sponsor start-up training to instruct the investigators and study coordinators. This session will give instruction on the protocol, the completion of the CRFs, and study procedures.
- make periodic visits to the study site
- be available for consultation and stay in contact with the study site personnel by mail, telephone, and/or fax
- review and evaluate CRF data and use standard computer edits to detect errors in data collection
- conduct a quality review of the database

In addition, Lilly or its representatives will periodically check a sample of the patient data recorded against source documents at the study site. The study may be audited by Lilly or its representatives, and/or regulatory agencies at any time. Investigators will be given notice before an audit occurs.

To ensure the safety of participants in the study, and to ensure accurate, complete, and reliable data, the investigator will keep records of laboratory tests, clinical notes, and patient medical records in the patient files as original source documents for the study. If requested, the investigator will provide Lilly, applicable regulatory agencies, and applicable ERBs with direct access to original source documents.

11.1. Data Capture System

An electronic data capture system will be used in this trial. The site maintains a separate source for the data entered by the site into the sponsor-provided electronic data capture system.

Case report form data will be encoded and stored in a clinical trial database. Data managed by a central vendor, such as laboratory test data, will be stored electronically in the central vendor's database system. Data will subsequently be transferred from the central vendor to the Lilly generic labs system.

Any data for which the paper documentation provided by the patient will serve as the source document will be identified and documented by each site in that site's study file. Paper documentation provided by the patient may include, for example, a paper diary to collect PRO measures (for example, a rating scale), a daily dosing schedule, or an event diary.

Data from complaint forms submitted to Lilly will be encoded and stored in the global product complaint management system.

12. Sample Size and Statistical Methods

12.1. Determination of Sample Size

The primary objective of this study is to compare abemaciclib versus docetaxel in terms of PFS in patients with Stage IV squamous cell carcinoma NSCLC after progression with a platinum-based therapy for advanced disease. The study will enroll approximately 150 patients in 2:1 randomization (100 patients in abemaciclib and 50 patients in docetaxel). The primary PFS analysis will be performed after 120 PFS events are observed (that is, 20% censoring rate). Historical information will be incorporated into control arm during the primary analysis by using a Bayesian approach. Assuming a hazard ratio (HR) of 0.64, with 150 patients and the proposed Bayesian design, power of 90.5% was estimated by simulation. Under a frequentist design, this sample size yields roughly 75% power with 1-sided type I error of 0.05.

If the true median PFS for the docetaxel arm is 3 months, the HR of 0.64 amounts to an approximately 1.7-month improvement in median PFS for the abemaciclib arm under an additional assumption of exponential survival distribution.

Refer to Attachment 6 for more detail on the statistical model and simulations.

12.2. Statistical and Analytical Plans

12.2.1. General Considerations

Statistical analysis of this study will be the responsibility of Lilly.

Efficacy analyses will be based on the intention-to-treat (ITT) analysis set. This population is defined as all patients randomized to study treatment. Patients will be grouped according to randomized treatment.

Safety analyses will be based on the Safety Population, defined as all enrolled patients receiving at least 1 dose of any study drug. Patients will be grouped according to treatment received in Cycle 1.

All tests of treatment effects will be conducted at a 2-sided alpha level of 0.05, unless otherwise stated. All tests of interactions will be conducted at a 2-sided alpha level of 0.1, and all CIs will be given at a 2-sided 95% level, unless otherwise stated.

Any change to the data analysis methods described in the protocol will require an amendment ONLY if it changes a principal feature of the protocol.

Any other change to the data analysis methods described in the protocol, and the justification for making the change, will be described in the clinical study report.

Additional exploratory analyses of the data will be conducted as deemed appropriate.

12.2.2. Patient Disposition

A detailed description of patient disposition will be provided. It will include a summary of the number and percentage of patients entered into the study, enrolled in the study, and treated as well as number and percentage of patients completing the study, or discontinuing (overall and by reason for discontinuation).

A summary of all important protocol deviations will be provided.

12.2.3. Patient Characteristics

Patient demographics, including age, sex, screening height and weight, and screening body mass index, will be reported using descriptive statistics.

Baseline disease characteristics will be summarized by presenting frequency counts and percentages for pathological diagnosis (histological or cytological), disease stage, or performance status.

Patient preexisting condition, historical illness, and prior chemotherapy (including both cytotoxic and targeted agents) will be summarized by treatment arm.

12.2.4. Concomitant Therapy

Concomitant medications will be summarized by treatment arm in a frequency table listing the terms recorded on the eCRF.

12.2.4.1. Postdiscontinuation Therapy

The numbers and percentages of patients reporting postdiscontinuation therapies will be provided overall, by type of therapy (surgery, radiotherapy, or systemic therapy), and by drug name.

12.2.5. Treatment Compliance

The number of dose omissions, reductions, delays, the number of cycles received, and dose intensity will be summarized for all treated patients per treatment arm.

Treatment compliance information for abemaciclib will be collected through solid oral dosage unit counts at each tumor assessment visit. The estimate of percent compliance will be given by:

$$\text{Percent Compliance} = \frac{\text{Actual cumulative dose taken}}{\text{Expected cumulative dose to be taken}} \times 100$$

The actual cumulative dose taken will be determined based on counting the number of dosage units returned at each visit and subtracting that number from the number of dosage units dispensed. The expected cumulative dose to be taken will be determined based on the assigned dose and taking into account any dose reductions or omissions.

12.2.6. Primary Outcome and Methodology

The primary endpoint of this study is PFS. PFS time is measured from the date of randomization to the date of investigator-determined objective progression as defined by RECIST v1.1, or death from any cause. Patients who have neither progressed nor died will be censored at the day of their last radiographic tumor assessment (if available) or date of randomization if no post initiation (that is, postbaseline) radiographic assessment is available. The detailed censoring rules are described below (Table JPBX.12.1).

The primary method of analysis for comparing PFS between the treatment arms will use a Bayesian exponential-likelihood model with a hierarchical random-effects distribution on treatment effects. The final model will incorporate historical data from a completed study (Garon et al. 2014) to augment the prospective control-arm data. If the Bayesian posterior probability of superiority of abemaciclib arm to docetaxel arm (that is, HR <1) exceeds 0.95, then it will be concluded that the experimental arm is superior. See Attachment 6 for more details. In addition to the primary analysis of PFS, following analysis will be conducted based on observed PFS data:

- Log-rank test will be used to compare the PFS distribution between treatment groups with and without adjustment using the same factors as the randomization scheme.
- Kaplan-Meier method (Kaplan and Meier 1958) will be used to estimate the PFS curve for each treatment group.
- The Cox proportional hazard model (Cox 1972) will be used to estimate the HR and corresponding 95% CI with and without stratified by randomization factors.

Table JPBX.12.1.   Rules for Determining Date of Progression or Censor for Progression-Free Survival

	Situation	Date of Progression or Censor	Outcome
1	No baseline tumor assessments	Date of Randomization	Censored
2	No post baseline assessments and no death	Date of Randomization	Censored
3	No documented progression and no death (with a post-baseline tumor assessment)	Date of last adequate tumor assessment	Censored
4	Patient lost to follow-up (or withdrew consent from study participation) before documented progression or death	Date of last adequate tumor assessment	Censored
5	Documented progression	Date of documented progression. If a tumor assessment was done on multiple days, use the earliest date for that visit.	Progressed
6	Death without documented progression	Date of death	Progressed
7	Death or documented progression after missed ≥2 consecutively post-baseline tumor assessment visits	Date of last adequate tumor assessment before missed assessments or date of randomization, whichever is later	Censored

12.2.7. Analyses of Efficacy

Secondary efficacy objective for this study include comparison of OS, ORR, DCR, and time to worsening of PS.

Kaplan-Meier analysis will be performed on the observed distribution of OS. Parameter estimates of the OS median and quartiles will be reported for each treatment group. All parameter estimates will be quoted together with their 95% confidence limits. Overall survival will be compared between treatment arms using the log-rank test.

The ORR and DCR of each treatment arm will be calculated as defined by RECIST v1.1. All rates will be compared between treatment arms based on a normal approximation for the difference between the rates.

Exploratory analysis may be performed to investigate associations between change in tumor size data and PFS and OS data.

12.2.8. Pharmacokinetic and Pharmacodynamic Analyses

PK analyses will be conducted on all patients who have received at least 1 dose of abemaciclib and have had samples collected (see Attachment 8).

Mean population PK parameters for abemaciclib in plasma (clearance, exposure, volume of distribution, and half-lives) and inter-individual PK variability will be computed using nonlinear mixed effect modeling (NONMEM). The current PK model for abemaciclib, which has been developed using plasma concentration data available from the Phase 1 Study JPBA, will be updated using the plasma data collected in this study. Covariate effects (such as age, weight, sex, and plasma protein levels) on the PK parameters of abemaciclib in plasma will also be investigated.

Pharmacodynamic biomarker samples will be collected as specified in the Study Schedule (Attachment 1). Refer to these attachments (including footnotes) for important information about these samples and their collection. Furthermore, pharmacodynamic data (such as neutrophil, lymphocytes, or platelets counts in blood, etc.) collected in this study may also be analyzed by means of NONMEM and connected to the population PK model in a PK/pharmacodynamic (PK/PD) model.

Pharmacodynamic data from all patients undergoing pharmacodynamic assessments will be analyzed. The pharmacodynamic data will be combined and exploratory analyses will be conducted to determine if a relationship exists between plasma concentration and pharmacodynamic effect(s) in humans. Interpatient variability in human pharmacodynamic response will also be assessed.

The version of software used for the analysis will be documented and will meet the Lilly requirements of software validation.

12.2.9. Biomarker Analysis

Associations between clinical endpoints and biomarkers will be evaluated using data from patients who have an evaluable sample for each biomarker of interest, and such evaluation will be done on an individual marker basis.

12.2.10.   Health Outcome/Quality of Life Analyses

Patient-reported outcomes are measured through paper versions of the following:

- MDASI-LC (includes additional page with 11 exploratory items that will be scored separately)
- EQ-5D-5L (EuroQol 5-Dimension 5 Level)

The reason and number of missing and incomplete questionnaires/assessments by visit will be summarized for each questionnaire and study arm.

12.2.10.1.   MDASI-LC

The MDASI-LC population will include all patients who completed at least 1 baseline assessment (that is, a completed baseline or a Cycle 1 MDASI-LC questionnaire completed before the administration of any study drug) followed by at least 1 MDASI-LC assessment after 1 cycle of study drug (for example, a completed MDASI-LC questionnaire at Cycle 2 Day 1 or later).

The MDASI-LC will be summarized for each assessment period and scored as described (Mendoza et al. 2011). The first 22 MDASI-LC items will be reported as core symptoms (Items 1-13), interference items (Items 14-19), and lung symptoms (Items 20-22). Eight of the 11 additional exploratory items will be reported as brain tumor symptoms derived from the MDASI-BT questionnaire (Items 23-30). The last 3 of the 11 exploratory items include 1 additional brain symptom (Item 31) and 2 treatment-expected toxicities (Items 32-33); each of these 3 items should be separately scored and reported (that is, no summated average is to be calculated across these 3 items).

For each patient in the MDASI-LC population (as described above), the maximum change from baseline score will be calculated and summarized for MDASI-LC composite scores (that is, Core Symptoms, Interference Items, Lung Symptoms with the Core Symptoms, and Brain Tumor Symptoms), the "worst pain" item, and separately for each of the last 3 exploratory items (Items 31-33).

Further analysis details will be described in the statistical analysis plan (SAP).

12.2.10.2.   Health State Utility

The EQ-5D-5L population will include all patients who completed at least 1 baseline assessment (that is, a completed baseline or a Cycle 1 EQ-5D-5L questionnaire completed before the administration of any study drug) followed by at least 1 completed EQ-5D-5L assessment after 1 cycle of study drug (for example, a completed EQ-5D-5L questionnaire at Cycle 2 Day 1 or later).

The EQ-5D-5L data will be scored based on EuroQol recommendations. The index score is calculated from a set of item weights to derive a score of <0 to 1, with 1 representing the best health status. The VAS is scored from 0 (worst imaginable health state) through 100 (best imaginable health state) to represent the patient's self-report for each day. EQ-5D-5L responses for each item will be summarized by frequency and corresponding percentages. Descriptive statistics for the index and VAS will be calculated as described in the SAP.

12.2.10.3.   Use of Pain Medications

Pain medication will be classified into 1 of 6 categories by the sponsor, using an analgesic ladder approach with medication category based on a World Health Organization scale outlined in Table JPBX.12.2. A therapy category for each cycle will be assigned according to the maximum category of analgesic agent(s) recorded in the Concomitant Form for that cycle. Categories of pain medication for each cycle (that is, categories for classification of NSAIDs and opioids and other non-opioid analgesics by level of strength to treat levels of pain severity according to Anatomical Therapeutic Chemical [ATC] classification code) will be determined based on ATC classification code as applied to the collected analgesic use data. Change in categories based on the analgesic ladder compared to baseline will be described by arm. Note that it may not be possible to distinguish opioids that were given parentally (coded as 4 in Table JPBX.12.2) from those that are also available orally and may have therefore been administered by mouth to be coded as 2 or 3 in Table JPBX.12.2. Information in the eCRF concerning pain medication may help distinguish the parenteral from the oral dosage form. For example, morphine is available as an injectable and is also available orally; here the relatively low parenteral mg strength (for example, 10 mg) could help distinguish from a 30- to 60-mg oral dosage form.

Table JPBX.12.2.   World Health Organization Pain Scale

Code	Description
0	No analgesia
1	Aspirin (for pain, not cardiovascular prophylaxis), acetaminophen, nonsteroidal anti-inflammatory drugs
2	Codeine, hydrocodone, pentazocine, oxycodone
3	Oral morphine, hydromorphone, methadone, transdermal fentanyl
4	Parenteral opiates
5	Neurosurgical procedures (blocks)

12.2.11.   Safety Analyses

All safety summaries and analyses will be based upon the Safety Population as defined in Section 12.2.1.

Overall exposure to study drug, the numbers of patients completing each cycle, and the dose intensity will be summarized using descriptive statistics. The number of patients with any dose adjustment will be presented for entire treatment period as well as for each cycle. The number of patients with dose reductions, dose delays, or dose omissions will also be summarized, as will the reasons for dose adjustments.

Adverse events will be reported using a unified CTCAE/MedDRA reporting process:

- The CTCAE v4.0 term reported by the investigator will be mapped to the MedDRA Preferred Term (PT) and System Organ Class (SOC) of the corresponding MedDRA Lower Level Term (LLT), unless the reported CTCAE term is 'Other – specify'.
- If the reported CTCAE term is 'Other – specify', the MedDRA LLT, PT, and SOC mapped from the verbatim AE term will be used.
- All listings and summaries will use the PT resulting from this process.

Preexisting conditions are defined as adverse events that begin prior to the first dose of study drug. A TEAE is defined as an event that first occurred or worsened in severity after baseline. Comparisons of preexisting conditions to on-treatment events at the LLT level will be used in the treatment-emergent computation.

An overall summary of AEs will be provided for AEs deemed by the investigator to be possibly related to study drug, and repeated for events regardless of study drug causality. Incidence rates of these events will be compared between treatment arms using Chi square test.

The following summaries will be produced by PT within SOC: preexisting conditions, SAEs, TEAEs, drug-related TEAEs, and procedure-related TEAEs.

The following summaries will be produced by PT within SOC and maximum CTCAE grade: laboratory-based TEAEs, nonlaboratory-based TEAEs, drug-related laboratory-based TEAEs, and drug-related nonlaboratory-based TEAEs.

Reasons for death will be summarized separately for on-therapy and within 30 days of treatment discontinuation. Serious adverse events will be summarized by PT.

Hospitalizations and transfusions during the study treatment period or during the 30-day short-term follow-up period will be summarized by treatment group.

12.2.12.   Subgroup Analyses

Subgroup analyses of PFS and OS will be performed for potential predictive and prognostic subgroup variables.

12.2.13.   Interim Analyses

No interim analyses are planned for this study. If an unplanned interim analysis is deemed necessary for reasons other than a safety concern, the protocol must be amended.

13. Informed Consent, Ethical Review, and Regulatory Considerations

13.1. Informed Consent

The investigator is responsible for ensuring that the patient understands the potential risks and benefits of participating in the study, including answering any questions the patient may have throughout the study and sharing in a timely manner any new information that may be relevant to the patient's willingness to continue his or her participation in the trial.

The ICF will be used to explain the potential risks and benefits of study participation to the patient in simple terms before the patient is entered into the study, and to document that the patient is satisfied with his or her understanding of the risks and benefits of participating in the study and desires to participate in the study.

The investigator is responsible for ensuring that informed consent is given by each patient or, where permitted by local law or regulation, by the patient's legal representative. This includes obtaining the appropriate signatures and dates on the ICF prior to the performance of any protocol procedures and prior to the administration of study drug.

As used in this protocol, the term "informed consent" includes all consent and assent given by patients or their legal representatives.

13.2. Ethical Review

Lilly or its representatives must approve all ICFs before they are used at the investigative sites. All ICFs must be compliant with the International Conference on Harmonisation (ICH) guideline on GCP.

Documentation of ERB approval of the protocol and the ICF must be provided to Lilly before the study may begin at the investigative sites.

The study site's ERBs should be provided with the following:

- the current IB or package labeling (for example, Package Insert, or SmPC) and updates during the course of the study
- the ICF
- relevant curricula vitae

13.3. Regulatory Considerations

This study will be conducted in accordance with:

- consensus ethics principles derived from international ethics guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
- ICH GCP Guideline (E6)
- applicable laws and regulations.

The investigator or designee will promptly submit the protocol to applicable ERB(s).

Some of the obligations of Lilly will be assigned to a third-party organization.

An identification code assigned to each patient will be used in lieu of the patient's name to protect the patient's identity when reporting AEs and/or other trial-related data.

13.3.1. Investigator Information

Physicians with a specialty in oncology will participate as investigators in this clinical trial.

13.3.2. Protocol Signatures

The sponsor's responsible medical officer will approve the protocol, confirming that, to the best of his or her knowledge, the protocol accurately describes the planned design and conduct of the study.

After reading the protocol, each principal investigator will sign the protocol signature page and send a copy of the signed page to a Lilly representative.

13.3.3. Final Report Signature

The clinical study report (CSR) coordinating investigator will sign the final CSR for this study, indicating agreement that, to the best of his or her knowledge, the report accurately describes the conduct and results of the study.

Lilly will select an investigator to serve as the CSR coordinating investigator.

The Lilly responsible medical officer and statistician will sign/approve the final CSR for this study, confirming that, to the best of his or her knowledge, the report accurately describes the conduct and results of the study.

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Attachment 1.   Protocol JPBX Study Schedule

Study Schedule, Protocol I3Y-MC-JPBX

Perform procedure as indicated.

Baseline Schedule		Study Period	Baseline		
		Visit	0		
		Duration	Up to 28 days		
		Relative Day	≤28	≤14	Relative to C1D1
Procedure Category	Procedure				Comments
Study Entry/ Enrollment	Informed Consent Form signed		X		Prior to conducting any protocol-specific tests / procedures
	Inclusion/Exclusion evaluation			X	
Medical History	Initial medical history/preexisting conditions			X	
	Historical illnesses			X	Including habits assessment of alcohol and tobacco use
Physical Examination	Physical examination			X	Including height and weight
	ECOG performance status			X	
	Vital signs			X	Includes blood pressure, pulse, respiratory rate, and temperature
Adverse Events Collection/CTCAE Grading			X		
Concomitant Medication Notation			X		Note: RANK-L or bisphosphonate agents should be initiated at least 7 days prior to randomization to study treatment, if applicable. For patients assigned to docetaxel, pretreatment with corticosteroids is recommended per label at least 3 days prior to first dose of docetaxel.
Tumor Assessment	Radiologic imaging according to RECIST 1.1		X		Performed locally. All patients, CT or MRI scan of the chest and abdomen. CT scan is the best currently available and reproducible method to measure lesions selected for response assessment; it is recommended that CT imaging of the abdomen be performed with IV contrast whenever possible. MRI may be used instead of CT in selected instances. Gadolinium-enhanced MRI is preferred if hypersensitivity to contrast.
	Brain MRI		X		Only those patients with symptoms of CNS involvement or known history of CNS metastasis must have brain MRI to confirm status of CNS metastases within 28 days of C1D1. The patient may have no evidence of Grade ≥1 CNS hemorrhage based on pretreatment MRI . A prior brain scan within 45 days of C1D1 may be used for baseline scan if no symptoms of CNS metastases.
	Tumor measurement (palpable or visible)		X		Photography of metastatic skin lesions with ruler required, if applicable

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Baseline Schedule		Study Period	Baseline		
		Visit	0		
		Duration	Up to 28 days		
		Relative Day	≤28	≤14	Relative to C1D1
Procedure Category	**Procedure**				**Comments**
Lab/ Diagnostic Tests	**Serum Pregnancy Test**			X	Local serum pregnancy test is performed on females with child-bearing potential.
	Central hematology			X	Enrollment and treatment decisions may be based upon results of tests performed locally. If local laboratory tests are used for this purpose, then a duplicate specimen must be submitted to the central laboratory. Discrepancies between local and central laboratory that may have an impact on eligibility or treatment decisions will not be considered protocol deviations.
	Central Chemistry			X	Enrollment and treatment decisions may be based upon results of tests performed locally. If local laboratory tests are used for this purpose, then a duplicate specimen must be submitted to the central laboratory. Discrepancies between local and central laboratory that may have an impact on eligibility or treatment decisions will not be considered protocol deviations.
	Local ECG			X	Abemaciclib patients will have a single copy baseline ECG. Patients must be supine (or reclined as flat as possible) for approximately 5 to 10 minutes before ECG.
	Archived Tumor Tissue			X	Archived Tissue is required for participation in study. Sample must be submitted for those patients who have met all inclusion/exclusion criteria before randomization can occur. A FFPE archived tumor tissue sample or 10-15 unstained slides (sample from block or core needle biopsy), cut at 5 microns (minimum of 10 slides) are required for randomization. Due diligence should be used to make sure that tumor specimen (not normal adjacent or tumor margins) is provided
Health Outcomes	**MDASI-LC; EQ-5D-5L**			X	Patients complete prior to extensive interaction with site staff.
Treatment Assignment	**IWRS randomization**			X	IWRS should be accessed at least 4 days prior to C1D1 to initiate pretreatment with dexamethasone for those patients randomized to docetaxel therapy per label recommendations. Archive tissue must be submitted before randomization can occur. Patients should begin treatment within 14 days of randomization.

Abbreviations: C1D1 = Cycle 1, Day 1; CNS = central nervous system ; CT = computed tomography; CTCAE = Common Terminology Criteria for Adverse Events; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; ; EQ-5D-5L = EuroQol 5 Dimension 5 Level; FFPE = formalin-fixed paraffin-embedded; IV = intravenous; IWRS = interactive web-response system; MDASI-LC = MD Anderson Symptom Inventory Lung Cancer; MRI = magnetic resonance imaging; RANK-L = nuclear factor kappa B ligand; RECIST = Response Evaluation Criteria in Solid Tumors.

On Treatment	Study Period	Study Treatment Period								
	Cycle/Visit	1		2		3		4-X		Comments
	Duration	21 days		21 days		21 days		21 days		A cycle is defined as the planned treatment interval of 21 days plus any subsequent delay prior to the start of the next cycle. A delay of a cycle due to holidays, weekends, bad weather, or other unforeseen circumstances will be permitted up to 7 days and not counted as a protocol deviation.
	Relative Day within Dosing Cycle	1	8	1	8	1	8	1	8	
Procedure Category	Procedure									Comments
Physical Examination	Weight	X		X		X		X		Weight is not required to be repeated on C1D1 if weight was collected within 3 days of C1D1 during baseline procedures.
	Vital signs	X		X		X		X		Includes blood pressure, pulse, respiratory rate, and temperature
	ECOG performance status	X		X		X		X		
Adverse Events Collection/CTCAE Grading		X		X		X		X		
Concomitant Medication Notation		X		X		X		X		
Lab/ Diagnostic Tests	Central hematology	X	X	X	X	X	X	X	X	Sample may be drawn within 72 hours prior to treatment on Day 1 of each cycle, and within ±2 business days at Day 8 of each cycle. If baseline sample was drawn within 72 hours of C1D1, it does not need to be repeated. If results of the laboratory tests obtained at planned Day 1 of the next cycle require a delay in the start of the subsequent cycle, any repeat laboratory tests should be obtained as clinically indicated. Local labs may be drawn for treatment adjustment and patient management purposes.
	Central chemistry	X	X	X	X	X	X	X	X	Sample may be drawn within 72 hours prior to treatment on Day 1 of each cycle, and within ±2 business days at Day 8 of each cycle. If baseline sample was drawn within 72 hours of C1D1, it does not need to be repeated. If results of the laboratory tests obtained at planned Day 1 of the next cycle require a delay in the start of the subsequent cycle, any repeat laboratory tests should be obtained as clinically indicated. Local labs may be drawn for treatment adjustment and patient management purposes
	Local Serum Pregnancy Test	X		X		X		X		For those females who are able to bear children, repeat pregnancy test should be done prior to administration of study treatment.

On Treatment	Study Period	Study Treatment Period								
	Cycle/Visit	1		2		3		4-X		
	Duration	21 days		21 days		21 days		21 days		A cycle is defined as the planned treatment interval of 21 days plus any subsequent delay prior to the start of the next cycle. A delay of a cycle due to holidays, weekends, bad weather, or other unforeseen circumstances will be permitted up to 7 days and not counted as a protocol deviation.
	Relative Day within Dosing Cycle	1	8	1	8	1	8	1	8	
Procedure Category	Procedure									Comments
Lab/ Diagnostic Tests	Pharmacokinetic sampling	X	X	X		X		X		See ECG and Pharmacokinetic Sampling Schedule (Attachment 8) for specific timing. No PK is required for patients assigned to docetaxel arm.
	Pharmacogenetic whole blood sample	X								
	Biomarker plasma sample	X		X						Draw sample before patient is dosed on C1D1 and upon arrival at site on C2D1.
	Local ECG (abemaciclib patients only)	X		X						For abemaciclib patients only: Single Copy. Predose on C1D1-Predose: C1D8: Upon arrival to site and 3 ± 0.5 h after first ECG collected this day: C2D1: Predose. Patients must be supine (or reclined as flat as possible) for approximately 5 to 10 minutes before ECG.
Tumor Assessment	Tumor measurement (palpable or visible)			X				X		Repeat every 6 weeks (every other even cycle) until documented progression and within 14 days of clinical progression. If skin lesions are noted, photography should be done with a digital camera and measured. Assessments may be completed ±3 days of scheduled cycle Day 1.
	Radiologic imaging according to RECIST (CT scan/MRI)					X		X		Performed locally. Patients will undergo radiographic assessment of disease status every 6 weeks (± 3 business days), as calculated from the first dose of study therapy until there is radiographic documentation of PD. Additionally, imaging should be performed within 14 days of clinical progression.
Health Outcomes	MDASI-LC; EQ-5D-5L	X		X		X		X		Patients complete prior to extensive interaction with site staff. Questionnaires should be administered on C1D1 and then Day 1 of every cycle thereafter.
Study Treatment	Abemaciclib	X		X		X		X		Dosed every 12 hours (± 2 hours) orally. The patient will receive D1 doses for each cycle in the clinic. On C1D8, patient will need to take abemaciclib 4 hours prior to schedule visit time for PK purposes.
	Docetaxel	X		X		X		X		Administered on Day 1 of every cycle, intravenously. Weight must be obtained prior to administration. Patient should be pretreated with corticosteroids per label recommendations.

Abbreviations: C1D1 = Cycle 1, Day 1; C1D8 = Cycle 1, Day 8; C2D1 = Cycle 2, Day 1; CNS = central nervous system; CT = computerized tomography ; CTCAE = Common Terminology Criteria for Adverse Events; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EQ-5D-5L = EuroQol 5 Dimension 5 Level; MDASI-LC = MD Anderson Symptom Inventory Lung Cancer; MRI = magnetic resonance imaging; PD = progressive disease; PK = pharmacokinetic; RECIST = Response Evaluation Criteria in Solid Tumors.

Post–Treatment Follow-up Period	Study Period	Short-term Follow-Up	Long-term Follow-Up	
	Visit	**801**	802-X	Post-Treatment Discontinuation Follow-Up should begin after the last dose of study therapy or, if study therapy has been omitted for an extended period, the date it is decided that the patient will not restart study therapy.
	Duration	30 +/- 7 days	Variable	Long-term follow-up begins the day after the short-term post-discontinuation follow-up visit (v801) is completed and continues until the patient's death, lost to follow-up, or overall study completion. The variable period depends on whether disease progression has occurred, and tumor assessments are due. Once disease progression has occurred visits should occur every 60 days
	Relative Day	**30**		

Procedure Category	Procedure			Comments
Physical Examination	**Weight**	X		
	Vital signs	X		Includes blood pressure, pulse, respiratory rate, and temperature
	ECOG performance status	X		
Tumor Assessment	**Tumor measurement (palpable or visible)**	X	X	Not required if progressive disease is documented while on treatment or at Visit 801. If the patient discontinues treatment and begins treatment with another anticancer therapy off study, scans will continue until progression or study ends. Reassessment should be repeated approximately every 6 weeks following the first dose of treatment until disease progression.
	Radiologic imaging according to RECIST	X	X	The same method of imaging used at baseline should be used for each subsequent assessment. Not required if PD is documented while on treatment or at Visit 801. If the patient discontinues treatment and begins treatment with another anticancer therapy off study, scans will continue until progression or study ends. During long-term follow-up period, repeat scans should performed approximately every 6 weeks until disease progression.
Survival information		X	X	Although preferable to collect during a clinic visit, survival information may be collected by contacting the patient or family directly (for example, via telephone) if no procedures required. This should be collected at minimum every 60 days if no other procedures are performed. Additional long-term follow-up data collection may include post-discontinuation anticancer therapies.
Adverse Events Collection/CTCAE Grading		X	X	After Visit 801, only study protocol or drug-related events are reported. If a patient has an ongoing AE or SAE possibly related to study drug (for instance, abnormal electrolytes), the patient should be followed until the event is resolved, the event is no longer considered to be drug-related, the event becomes stable or returns to baseline, a new treatment is initiated for the patient, or the patient dies or is lost to follow-up. Any subsequent follow-up(s) for AEs will be no more than 30 days ± 5 days in duration.
Concomitant Medication Notation		X		

Post– Treatment Follow-up Period	Study Period	Short-term Follow-Up	Long-term Follow-Up	
	Visit	801	802-X	Post-Treatment Discontinuation Follow-Up should begin after the last dose of study therapy or, if study therapy has been omitted for an extended period, the date it is decided that the patient will not restart study therapy.
	Duration	30 +/- 7 days	Variable	Long-term follow-up begins the day after the short-term post-discontinuation follow-up visit (v801) is completed and continues until the patient's death, lost to follow-up, or overall study completion. The variable period depends on whether disease progression has occurred, and tumor assessments are due. Once disease progression has occurred visits should occur every 60 days
	Relative Day	30		
Procedure Category	**Procedure**			**Comments**
Lab/ Diagnostic Tests	Central Hematology	X		
	Central Chemistry	X		
	Local Serum Pregnancy Test	X		For those females who are able to bear children
	Plasma Biomarker	X		
	Local ECG	X		Only for patients randomized to abemaciclib
Health Outcomes	MDASI-LC, EQ-5D-5L	X		Patients complete prior to extensive interaction with site staff.

Abbreviations: AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EQ-5D-5L = EuroQol 5 Dimension 5 Level; IV = intravenous; MDASI = MD Anderson Symptom Inventory Lung Cancer; MRI = magnetic resonance imaging; PD = progressive disease; PK = pharmacokinetic; RECIST = Response Evaluation Criteria in Solid Tumors; SAE = serious adverse event.

Study Schedule for the Continued Access Period			Patients on Study Treatment	Continued Access Period Follow-Up	Comments
		Cycle	X	Follow-Up[a]	
		Visit	501-5XX	901	
		Duration (days)	21	30(+/- 5 days)	
		Relative day within a cycle	1		
Procedure Category	Procedure				
Lab	Local Serum Pregnancy Test		X	X	For those females with child bearing potential. Repeat pregnancy test should be done at each cycle prior to administration of study treatment.
Adverse Events Collection/CTCAE Grading[b]			X	X	
Study Treatment	Abemaciclib[c]		X		Only for those that were assigned to abemaciclib at randomization will continue to receive abemaciclib orally every 12 hours until criteria for discontinuation is met.
	Docetaxel[d]		X		Patients assigned to docetaxel may continue to received docetaxel intravenously on Day 1 of every cycle until criteria for discontinuation is met.

Abbreviations: AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; SAE = serious adverse event.

[a]   The continued access period begins after study completion (that is, after final OS analysis) and ends at the end of trial (that is the last patient visit).

[b]   Data on SAEs that occur before the end of trial will be stored in the collection database and the Lilly Safety System. Only related SAE/AEs will be reported while the patient continues to receive treatment.

[c]   Abemaciclib is to be administered every 12 hours on Days 1 through 21 of each cycle for those that have received abemaciclib treatment on study until a criteria for discontinuation is met.

[d]   Docetaxel is to be administered once every 3 weeks on Day 1 of each cycle for those that have received docetaxel treatment on study until a criteria for discontinuation is met.

Attachment 2.   Protocol JPBX Clinical Laboratory Tests

Clinical Laboratory Tests

Hematology[a]	Clinical Chemistry[a] (except as indicated)
Hemoglobin	**Serum Concentrations of:**
Hematocrit	Sodium
	Potassium
Erythrocyte count (RBC)	Total bilirubin
Mean cell volume (MCV)	Direct bilirubin
Mean cell hemoglobin concentration (MCHC)	Alkaline phosphatase
Leukocytes (WBC)	Alanine aminotransferase (ALT)
Neutrophils, segmented and bands	Aspartate aminotransferase (AST)
Lymphocytes	Blood urea nitrogen (BUN)
Monocytes	Creatinine
	Chloride
Eosinophils	Calcium
Basophils	Albumin
Platelets	Total Protein
	Glucose (random)
	Lactase Dehydrogenase (LDH)
	Calculated creatinine clearance ≥ 50 mL/min (per the Cockcroft-Gault formula or equivalent, Attachment 5)
	Serum Pregnancy Test (females only)[b] (local only)

Abbreviations: RBC = red blood cells; WBC = white blood cells.

[a]   Assayed by Lilly-designated (central) laboratory.

[b]   Assayed by investigator-designated (local) laboratory.

___

Attachment 3.   Protocol JPBX Hepatic Monitoring Tests for Treatment-Emergent Abnormality

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Selected tests may be obtained in the event of a treatment-emergent hepatic abnormality and may be required in follow up with patients in consultation with the Lilly clinical research physician.

Hepatic Monitoring Tests

Hepatic Hematology[a]	Haptoglobin[a]
Hemoglobin	
Hematocrit	**Hepatic Coagulation[a]**
RBC	Prothrombin Time
WBC	Prothrombin Time, INR
Neutrophils, segmented and bands	
Lymphocytes	**Hepatic Serologies[a,b]**
Monocytes	Hepatitis A antibody, total
Eosinophils	Hepatitis A antibody, IgM
Basophils	Hepatitis B surface antigen
Platelets	Hepatitis B surface antibody
	Hepatitis B Core antibody
Hepatic Chemistry[a]	Hepatitis C antibody
Total bilirubin	Hepatitis E antibody, IgG
Direct bilirubin	Hepatitis E antibody, IgM
Alkaline phosphatase	
ALT	**Anti-nuclear antibody[a]**
AST	
GGT	**Anti-smooth muscle antibody[a]**
CPK	

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; CPK = creatine phosphokinase; GGT = gamma glutamyl transferase; Ig = immunoglobulin; INR = international normalized ratio; RBC = red blood cells; WBC = white blood cells.

[a] Assayed by Lilly-designated laboratory.

[b] Reflex/confirmation dependent on regulatory requirements and/or testing availability.

Attachment 4. Protocol JPBX ECOG Performance Status

Eastern Cooperative Oncology Group (ECOG) Performance Status

Activity Status	Description
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead.

Source: Oken et al. 1982.

Attachment 5. Protocol JPBX Creatinine Clearance Formula

Note: This formula is to be used for calculating creatinine clearance (CrCl) from **local laboratory results only.**

For serum creatinine concentration in mg/dL:

$$\text{CrCl (mL/min)} = \frac{(140 - \text{age}^a) \times (\text{wt}) \times 0.85 \text{ (if female)}, \text{ or} \times 1.0 \text{ (if male)}}{72 \times \text{serum creatinine } (mg/dL)}$$

For serum creatinine concentration in $\mu mol/L$:

$$\text{CrCl (mL/min)} = \frac{(140 - \text{age}^a) \times (\text{wt}) \times 0.85 \text{ (if female)}, \text{ or} \times 1.0 \text{ (if male)}}{0.81 \times \text{serum creatinine } (\mu mol/L)}$$

[a] Age in years, weight (wt) in kilograms.
Reference: Cockcroft and Gault 1976.

Attachment 6.   Protocol JPBX Details of Statistical Progression-Free Survival Model and Simulation Result

For this study, we use a Bayesian Augmented Control (BAC) model that allows information borrowing from a previous study to augment the data on the control arm in the current study. The primary endpoint of this trial is progression-free survival (PFS) time. PFS is modeled using an exponential-likelihood model (constant baseline hazard) as specified below:

$$\lambda_T = \lambda \exp(\theta_T)$$

$$\lambda \sim Gamma(\alpha, \beta)$$

$$\theta_T \sim Normal(\mu_0, \sigma_0^2)$$

where λ_T is the hazard rate for the experimental arm, and λ is the hazard rate for the current control arm. θ_T is the log hazard ratio (HR) between the 2 hazard rates.

The model used for incorporating the historical controls is as follows:

$$\lambda_1 = \lambda \exp(\gamma_1)$$

where λ_1 is the hazard rate for the historical control, λ is as above, and γ_1 is the log HR between the 2 hazard rates.

The following hierarchical model is used,

$$\gamma_1 \sim Normal(\mu_\gamma, \tau^2)$$

and we specify priors for the hyperparameters:

$$\mu_\gamma \sim Normal(m_\gamma, t_\gamma^2)$$

$$\tau^2 \sim InverseGamma(a_\gamma, b_\gamma)$$

We use the relatively uninformative priors of Normal (0, 100) for the normally distributed parameters. For the Inverse Gamma prior for τ^2, we chose a distribution with mean of 0.1 and with equivalent weight of 0.03 to enable borrowing of approximately 40 patients from historical data when true control hazard rate is consistent with historical control hazard rate, that is, $\tau^2 \sim$ Inverse Gamma(0.015, 0.00015). This is consistent with the prior opinion that the standard deviation of the log(HR) of the assumed population of historical studies relative to current control arm is 0.1.

The mathematical details to assess the amount of borrowing are as follows: since the mean (μ) and variance (σ^2) of the hazard rate (λ) are $\alpha\beta$ and $\alpha\beta^2$, respectively, then the quantity $(\mu/\sigma)^2$ reproduces α. We can compute α for each trial and mean α across each simulated scenario. These simulations are performed across a grid of "true" values for λ under the case of

"borrowing" and "no borrowing," where the "no borrowing" case is achieved by simulating under a large value for the mean of τ. The difference between the mean α's for each true λ on the grid provides an estimate of the equivalent number of events attributable to borrowing. This value is plotted against true lambda to show how much borrowing occurred based on the chosen study design.

Historical Controls

In the REVEL study (Garon et al. 2014), NSCLC patients were randomized to either docetaxel plus ramucirumab or docetaxel monotherapy after receiving first-line platinum based therapy. A total of 1253 patients were randomized with 628 assigned to ramucirumab plus docetaxel and 625 patients assigned to placebo plus docetaxel, with the squamous population being 157 and 171 respectively. We use data from all squamous patient randomized to docetaxel monotherapy arm. CCI
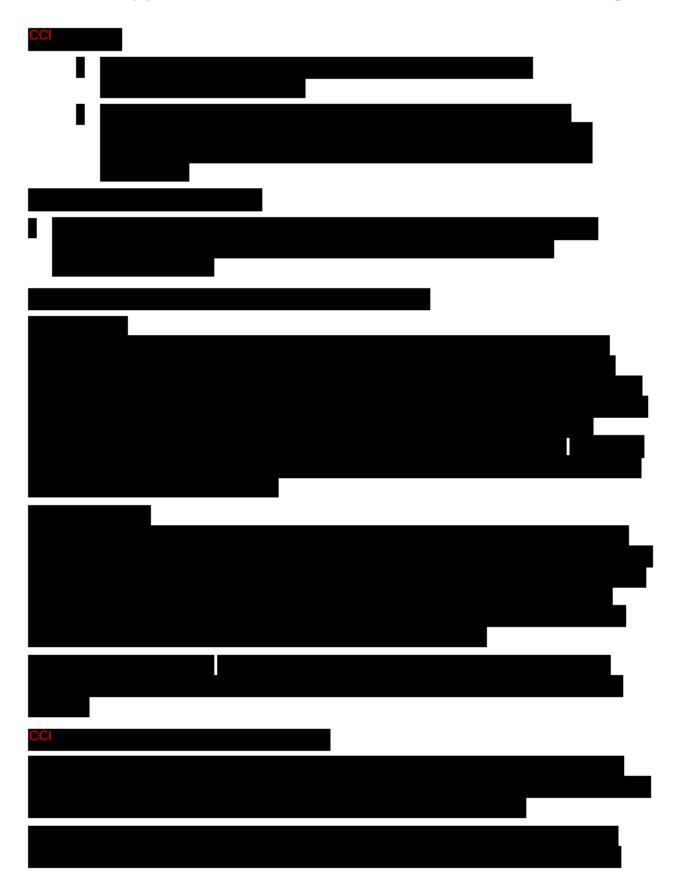
Operating Characteristics

In this study, the experimental therapy will be considered superior to control if the posterior probability that the HR for PFS of experimental versus control is <1 is >95% or, formally, if Pr(Treatment HR <1) >95%. Table 1 shows the operating characteristics that correspond to this decision rule. These results are based on 1,000 simulated trials per scenario, and N=150 patients randomized 2:1 favoring the experimental arm for each trial. For purposes of simulation, the accrual rate is assumed to be 2 patients per week, and the final efficacy analysis will be performed 12 months after the last patient is enrolled.

We show operating characteristics under 2 different assumptions of the true hazard rate in the current control arm in Table 1. The probability of success is calculated for study designs with BAC and without BAC. Under the assumption that the current control arm has the same PFS hazard rate as the historical controls CCI the BAC design will have about 90.5% power to detect an HR of 0.64 with a Type I error rate of 5.5%. Without BAC design, this study would have only 76.1% power. Hence, the BAC design substantially improves operating characteristics compared to standard designs.
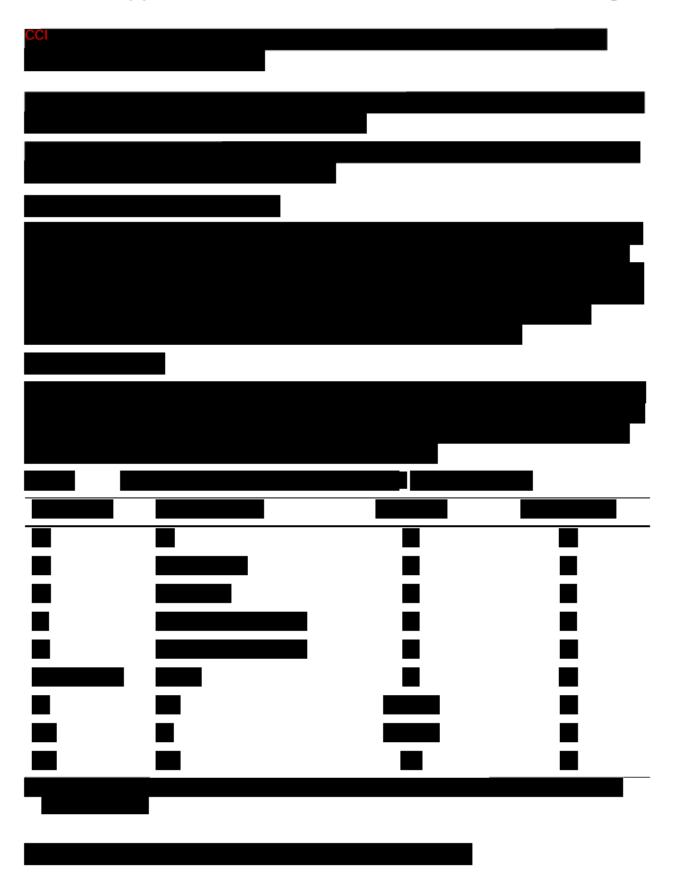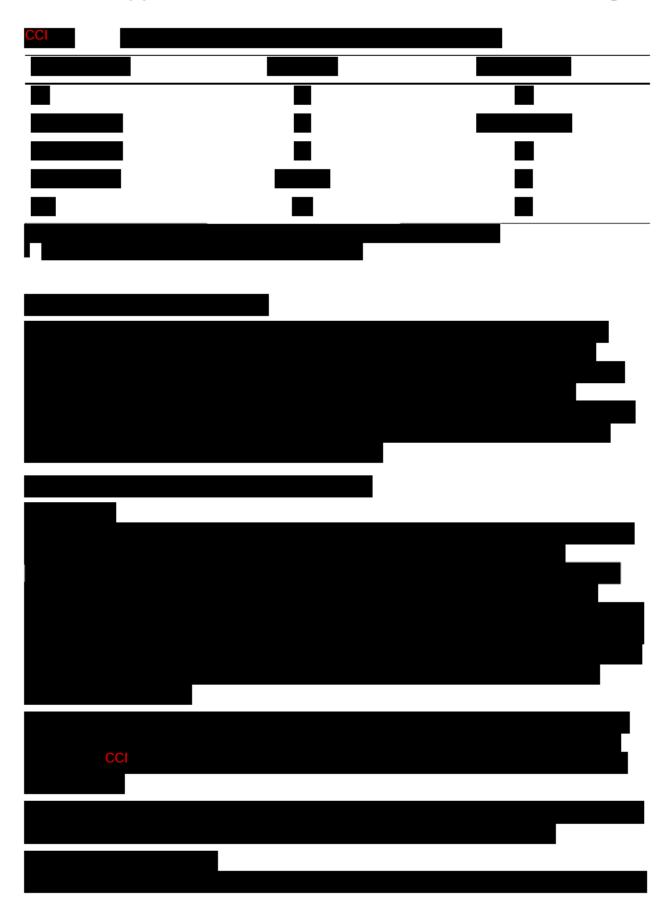
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Attachment 7.   Protocol JPBX RECIST Criteria 1.1

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Attachment 8.   Protocol JPBX Pharmacokinetic and ECG Sampling Schedule

It is essential that the exact time of abemaciclib dose on the day of PK sampling and the 3 days prior to the PK sample is recorded on the appropriate form according to the instructions provided. The exact time of collection of each venous blood sample must also be recorded on the appropriate form. Aberrations to specified ECG and sampling times will not be considered protocol deviations as long as the ECG and samples are taken and the actual ECG and sampling time is recorded.

Pharmacokinetic and ECG Sampling Schedule for Abemaciclib Patients Only

Cycle (C) and Day (D)	ECG Collection	PK Sample Number	Dosing of Abemaciclib	Sampling Time for ECG and PK from Blood[a]
Baseline (Day -14 to Day -1)	X			
C1D1	X	1	X	Pre-dose (0 h)[c]
C1D8	X	2	X[b]	At least 4 hrs after taking abemaciclib dose at home (that is, upon arrival at site)[d]
C1D8	X	3		3 ± 0.5 h after PK Sample Number 2 (that is, at least 7 ± 0.5 h after taking abemaciclib dose at home)
C2D1	X	4	X	Pre-dose (0 h)[c]
C2D1		5		3 ± 0.5 h after abemaciclib dose
C3D1		6	X	Pre-dose (0 h)[c]
C4D1		7	X	Pre-dose (0 h)[c]
30-Day Follow- up	X			

Abbreviations: C = Cycle; D = Day; h = hour(s); ECG = electrocardiogram; PK = pharmacokinetic.

[a] Samples of approximately 2 mL of whole blood will be drawn for measurement of abemaciclib and its metabolites.

[b] On Cycle 1 Day 8 only, patient should take abemaciclib dose at home at least 4 h before arrival at site. The time of abemaciclib dose intake must be recorded that day.

[c] Patient is administered abemaciclib in the clinic after required pre-dose ECG and/or PK sample is obtained

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Attachment 9.   Protocol JPBX Sampling Summary

This table summarizes the maximum number of samples (venipunctures, biopsies), volumes for all sampling, and tests (study qualification, health monitoring, drug concentration, pharmacodynamics/tailoring biomarkers) during the study. The summary below provides estimates. More samples could be required in the case of retests, additional health monitoring (if needed), or for patients continuing treatment beyond the protocol-specified number of cycles in the study. Fewer samples may actually be taken (for example, patients who discontinue from the study).

Protocol I3Y-MC-JPBX Sampling Summary[a]

Purpose	Sample Type	Maximum Amount per Sample	Maximum Number Samples	Maximum Total Amount
Health monitoring[a]	Blood for Chemistry	2.5 mL	14	35 mL
	Blood for Hematology	2.0 mL	14	28 mL
Drug concentration	Plasma	2 mL	7	14 mL
Pharmacodynamic and/or other biomarkers	Plasma	6 mL	3	18 mL
Stored sample for pharmacogenetic evaluations	Whole Blood	10 mL	1	10 mL
Hepatic monitoring[b]	Blood	3 - 30 mL	-	-
Biomarkers, tissue	FFPE tumor tissue slides or block	FFPE tumor tissue slides OR FFPE tumor block	10-15 unstained slides or a tissue block	FFPE tumor tissue slides or block
Total blood volume				105 mL

Abbreviation: FFPE = formalin-fixed, paraffin embedded.

[a]   Covers baseline, Cycles 1 through 6, plus V801.

[b]   Based on laboratory safety values, unscheduled hepatic monitoring testing may be performed as part of patient follow-up, in consultation with the designated medical monitor.

Attachment 10. Protocol JPBX Inducers and Strong Inhibitors of CYP3A

The information in this table is provided for guidance to investigators and does not preclude the use of these medications if clinically indicated.

Strong Inducers of CYP3A
Carbamazepine
Dexamethasone[a]
Phenobarbital/phenobarbitone
Phenytoin
Rifapentine
Rifampin
Rifabutin
St John's wort

Moderate Inducers of CYP3A
Bosentan
Lenisurad
Modafinil
Primidone
Telotristat ethyl

Strong Inhibitors of CYP3A
Aprepitant
Ciprofloxacin
Clarithromycin
Conivaptan
Diltiazem
Erythromycin
Fluconazole
Itraconazole
Ketoconazole
Nefazodone
Posaconazole
Troleandomycin
Verapamil

[a] Important note: All patients may receive supportive therapy with dexamethasone, preferably ≤7 days, if clinically indicated.

Attachment 11.   Protocol JPBX CTCAE 4.03 Definitions for Diarrhea and Interstitial Lung Disease

Diarrhea will be evaluated in this study using the criteria proposed by Common Terminology Criteria for Adverse Events (CTCAE) v4.0 revised: CTCAE 4.03-June 14, 2010: Gastrointestinal disorders.

Gastrointestinal Disorders					
Grade					
Adverse Event	1	2	3	4	5
Diarrhea	Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline.	Increase of 4-6 stools per day over baseline; moderate increase in ostomy output compared to baseline	Increase ≥7 stools per day over baseline; incontinence; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self-care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: a disorder characterized by frequent and watery bowel movements					

Abbreviation: ADL = Activities of Daily Living.

Interstitial lung disease/pneumonitis will be evaluated in this study using the criteria proposed by CTCAE v4.0 revised: CTCAE 4.03–June 14, 2010: Respiratory, thoracic, and mediastinal disorders.

Respiratory, Thoracic, and Mediastinal Disorders					
Grade					
Adverse Event	1	2	3	4	5
Pneumonitis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated; limiting instrumental ADL	Severe symptoms; limiting self-care ADL; oxygen indicated	Life-threatening respiratory compromise; urgent intervention indicated (e.g., tracheotomy or intubation)	Death
Definition: a disorder characterized by inflammation focally or diffusely affecting the lung parenchyma					

Abbreviation: ADL = Activities of Daily Living.

Attachment 12.   Protocol JPBX Amendment(b) Summary A Randomized Phase 2 Study of Abemaciclib (LY2835219) versus Docetaxel in Patients with Stage IV Squamous Non-Small Cell Lung Cancer Previously Treated with Platinum-Based Chemotherapy

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Overview

Study I3Y-MC-JPBX, a Randomized Phase 2 Study of Abemaciclib (LY2835219) versus Docetaxel in Patients with Stage IV Squamous Non-Small Cell Lung Cancer Previously Treated with Platinum-Based Chemotherapy, has been amended. The new protocol is indicated by Amendment (b) and will be used to conduct the study in place of any preceding version.

The overall changes and rationale for the changes made to this protocol are as follows:

- Interstitial lung disease (ILD) and multidrug and toxin extrusion protein (MATE) were added to the list of abbreviations (Section 4).
- Rationale for Amendment (b) was added (Section 5.4).
- References to study drug were modified in Sections 9.2, 9.7, and 12.2.5.
- Table JPBX.9.2 was updated with dose adjustment criteria for ILD/pneumonitis.
- Section 9.4.2.1.2.2 was updated to reflect the addition of ILD/pneumonitis dose modifications.
- ILD/pneumonitis dose modifications (Section 9.4.2.1.2.5) and safety monitoring guidance were added (Section 10.3.3.4).
- Section 9.6 was modified to align with updates to the Investigator's Brochure.
- Attachment 10 was updated to include additional CYP3A inducers and inhibitors.
- CTCAE 4.03 Grade definitions for ILD/pneumonitis were added in Attachment 11.

Minor typographical and formatting edits were made throughout the document for clarity and consistency.

Revised Protocol Sections

Note:	All deletions have been identified by ~~strikethroughs~~.
	All additions have been identified by the use of <u>underscore</u>.

4. Abbreviations and Definitions

Term	Definition
…	
ILD	interstitial lung disease
…	
MATE	multidrug and toxin extrusion protein
…	

5.4.   Rationale for Amendment (b)

Study JPBX protocol was amended to update the safety monitoring and guidance for interstitial lung disease (ILD)/pneumonitis. Changes to the dose adjustment and delay section and Table JPBX.9.2 were done to specify dose modifications in response to ILD/pneumonitis events. These updates are in alignment with changes made in the development core safety information of the IB.

The protocol was updated to bring references to abemaciclib into alignment with the sponsor's standard language.

Section 9.6 (Concomitant Therapy) was updated to align with the current IB. Additional language was added cautioning against concomitant use of abemaciclib and substrates of the following:
- P-glycoprotein
- breast cancer resistance protein
- organic cation transporter 2
- multidrug and toxin extrusion protein 1 (MATE1), and
- MATE2-K

Substrates of these transporters, including metformin, digoxin, and dofetilide, should be substituted or avoided.

The Concomitant Therapy (Section 9.6) was also updated to remove cautionary language regarding coadministration of narrow therapeutic index CYP substrate drugs. This is based on a clinical study (Study I3Y-MC-JPCB) which found no meaningful effect of abemaciclib on the pharmacokinetics of CYP substrates, namely caffeine [CYP1A2], S-warfarin [CYP2C9], midazolam [CYP3A], and dextromethorphan [CYP2D6].

The list of Inducers and Strong Inhibitors of CYP3A (Attachment 10) was also modified to reflect updated guidance.

Minor typographical and formatting edits were made throughout the document for clarity and consistency.

9.2.   Materials and Supplies

Abemaciclib will be supplied by Lilly ~~as capsules~~ for oral administration. Abemaciclib ~~capsules~~ should be stored according to the temperature range listed on the product label, and should not be opened, crushed, or chewed.

9.4.2.1.   Dose Adjustments and Delays

Table JPBX.9.2.   Toxicity Dose Adjustments and Delays of Abemaciclib for Study JPBX

Toxicity Type	Dose Adjustment Guidelines	Dose Action	Dose Change
…			
Nonhematologic Toxicity[a] (except diarrhea, ~~and~~ ALT increased, and ILD/Pneumonitis) Section 9.4.2.1.2.2	Persistent or recurrent[b] Grade 2 that does not resolve with maximal supportive measures within 7 days to baseline or Grade 1	Dose **MUST** be suspended until toxicity resolves to either baseline or Grade 1.	Dose **MUST** be reduced by one dose level.
Nonhematologic Toxicity (except diarrhea, ALT increased, and ILD/Pneumonitis) Section 9.4.2.1.2.2	Grade 3 or 4	Dose **MUST** be suspended until toxicity resolves to either baseline or Grade 1.	Dose **MUST** be reduced by one dose level.
...			
ALT Increased with increased total bilirubin, in the absence of cholestasis Sections 9.4.2.1.2.4 and 10.3.3.1	Grade 3 increased ALT (>5.0× ~~x~~ ULN) with total bilirubin >2× ~~x~~ ULN	Abemaciclib **MUST** be discontinued	Abemaciclib **MUST** be discontinued.
ILD/Pneumonitis Sections 9.4.2.1.2.5 and 10.3.3.4	Grade 2 that persists or recurs despite maximal supportive measures and does not return to baseline or Grade 1 within 7 days	Dose **MUST** be suspended until toxicity resolves to baseline or Grade ≤1.	Dose **MUST** be reduced by 1 dose level.
ILD/Pneumonitis Sections 9.4.2.1.2.5 and 10.3.3.4	Grade 3 or 4	Abemaciclib **MUST** be discontinued.	Abemaciclib **MUST** be discontinued.

Abbreviations: ALT = alanine transaminase; ASCO = American Society of Clinical Oncology; ILD = interstitial lung disease; ULN = upper limit of normal.

Note: MAY = per the investigator's clinical judgment; MUST = mandatory.

[a]   Additional guidance for hepatic and renal monitoring is in Sections 10.3.3.1 and 10.3.3.2.

ᵇ Determination of persistent events will be at the discretion of the investigator. Recurrent toxicity refers to the same event occurring within the next 8 weeks (as measured from the stop date of the preceding event). As a general guidance, based on the risk/benefit balance assessment per the investigator, for a patient who experiences a new episode of Grade 3 hematological toxicity after more than 8 weeks following the last episode of same Grade 3 hematological toxicity, the investigator may consider resuming the patient on the same drug dose should the patient satisfy the following conditions:
- shows stable hematological counts (Grade ≤2) during that timeframe
- has absence of any signs or risk of infection
- is benefiting from study treatment

ᶜ Note: the patient who presents with no liver metastases at baseline.

ᵈ Grade 3 ALT increased is a trigger for additional assessments and possibly hepatic monitoring. See Section 10.3.3.1 for additional guidance for hepatic monitoring

9.4.2.1.2.2. Nonhematologic Toxicity (except diarrhea)

Refer to Section 9.4.2.1.2.3 for guidance and supportive measures of diarrhea toxicity possibly related to abemaciclib, or Sections 9.4.2.1.2.4 and 10.3.3.1 for additional hepatic monitoring safety and monitoring guidance, and Sections 9.4.2.1.2.5 and 10.3.3.4 for ILD/pneumonitis guidance. If a patient experiences ≥Grade 3 nonhematologic toxicity (except diarrhea, refer to Section 9.4.2.1.2.3; or ALT increased, refer to Sections 9.4.2.1.2.4 and 10.3.3.1 to Section 10.3.3.1; ILD/pneumonitis, refer to Sections 9.4.2.1.2.5 and 10.3.3.4) possibly related to abemaciclib, then dosing must be suspended (until the toxicity resolves to either baseline or at least Grade 1) and the dose of abemaciclib must be reduced as outlined in Table JPBX.9.3.

If a patient experiences persistent or recurrent Grade 2 nonhematologic toxicity (except diarrhea, refer to Section 9.4.2.1.2.3; ALT increased, refer to Sections 9.4.2.1.2.4 and 10.3.3.1; ILD/pneumonitis, refer to Sections 9.4.2.1.2.5 and 10.3.3.4)(except diarrhea, refer to Section 9.4.2.1.2.3 or ALT increased, refer to Section 10.3.3.1) possibly related to abemaciclib that does not resolve with maximal supportive measures within 7 days to either baseline or Grade 1, then dosing must be suspended (until the toxicity resolves to either baseline or at least Grade 1) and the dose of abemaciclib must be reduced as outlined in Table JPBX.9.3.

9.4.2.1.2.5. Interstitial Lung Disease/Pneumonitis

Dose modifications and management for ILD/pneumonitis are provided in Table JPBX.9.2. For persistent or recurrent Grade 2 ILD/pneumonitis that does not resolve with maximal supportive measures within 7 days to baseline or Grade 1, treatment with abemaciclib must be suspended until the toxicity resolves to baseline or Grade 1 and the dose must be reduced by 1 dose level. For Grade 3 or 4 ILD/pneumonitis, the patient must be discontinued from abemaciclib. Refer to Section 10.3.3.4 for additional ILD/pneumonitis monitoring guidance.

9.6. Concomitant Therapy

…

Abemaciclib is extensively metabolized through oxidation by cytochrome P450 (CYP) 3A. In clinical drug interaction studies, coadministration of clarithromycin, a strong CYP3A inhibitor, increased exposure (area under the concentration-time curve) to abemaciclib by 3.4-fold (Study

I3Y-MC-JPBE) and coadministration of rifampin, a strong CYP3A inducer, decreased exposure to abemaciclib by 95% (Study I3Y-MC-JPBF). Therefore, grapefruit or grapefruit juice as well as inducers and inhibitors of CYP3A should be substituted or avoided if possible (Attachment 10). Although dexamethasone is a CYP3A4 inducer, use during the study is allowed. The dose of corticosteroids, including dexamethasone, will be captured throughout the study.

~~In vivo in humans, abemaciclib is extensively metabolized through oxidation. Additionally, the results from an in vitro human recombinant cytochrome P450 (CYP) phenotyping study indicate that oxidative metabolism of abemaciclib is primarily catalyzed by CYP3A4. Based on these findings, grapefruit juice as well as inducers and strong inhibitors of CYP3A4 should be substituted or avoided if possible (Attachment 10). Although dexamethasone is a CYP3A4 inducer, use during the study is allowed. The dose of corticosteroids, including dexamethasone, will be captured throughout the study.~~

Abemaciclib can be coadministered with drugs that are substrates of CYP enzymes.

Abemaciclib and/or its major metabolites inhibit the efflux transporters P-glycoprotein and breast cancer resistance protein and renal transporters organic cation transporter 2, MATE1, and MATE2-K at clinically relevant concentrations. Therefore, substrates of these transporters such as metformin and those with a narrow therapeutic index such as digoxin and dofetilide should be substituted or avoided if possible.

~~In addition, in vitro studies in cultured human hepatocytes indicate that abemaciclib and its major metabolites LSN2839567 and LSN3106726 down regulate mRNA of 1 or more CYPs, including CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2D6, and CYP3A, at clinically relevant concentrations. The mechanism of down regulation and its clinical relevance are presently not understood. Therefore, care should be taken when coadministering substrate drugs of the above CYPs with narrow therapeutic margin (Attachment 10).~~

Docetaxel is a CYP3A4 substrate. ~~In vitro studies have shown that the metabolism of docetaxel may be modified by the concomitant administration of compounds that induce, inhibit, or are metabolized by cytochrome P450 3A4. In vivo studies showed that the exposure of docetaxel increased 2.2-fold when it was coadministered with ketoconazole, a potent inhibitor of CYP3A4. Protease inhibitors, particularly ritonavir, may increase the exposure of docetaxel. Concomitant use of docetaxel injection and drugs that inhibit CYP3A4 may increase exposure to docetaxel and should be avoided.~~ Grapefruit juice as well as inducers and strong inhibitors of CYP3A4 should be substituted or avoided if possible (Attachment 10). If systemic administration of a CYP3A4 inhibitor cannot be avoided ~~I~~in patients receiving treatment with docetaxel injection, consider close monitoring for toxicity and/or ~~a~~ docetaxel injection dose reduction. ~~could be considered if systemic administration of a potent CYP3A4 inhibitor cannot be avoided. Grapefruit juice as well as inducers (for example, phenytoin and carbamazepine) and strong inhibitors of CYP3A4 should be substituted or avoided if possible (Attachment 10).~~ The dose of corticosteroids, including dexamethasone, will be captured throughout the study.
…

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9.7.   Treatment Compliance

...

Abemaciclib compliance will be assessed by counting returned ~~capsules~~solid oral dosage units. Study medication administration data will be recorded in the patient's medical record and eCRF.

10.3.3.4 Interstitial Lung Disease/Pneumonitis

Interstitial lung disease/pneumonitis has been identified as an adverse drug reaction for abemaciclib. The majority of events observed in clinical trials were Grade 1 or Grade 2 with serious cases and fatal events reported. Additional information is available in the IB.

Ask your patients to report any new or worsening pulmonary symptoms such as dyspnea, cough, and fever, and investigate and treat as per your local clinical practice (including corticosteroids as appropriate). If ILD/pneumonitis is suspected, investigations may include imaging, such as high-resolution computed tomography, broncheoalveolar lavage, and biopsy as clinically indicated.

Refer to Table JPBX.9.2 for guidance on dose adjustments of abemaciclib for patients with ILD/pneumonitis (see Attachment 11 for ILD/pneumonitis CTCAE grades). Discontinue abemaciclib in cases of severe ILD/pneumonitis.

12.2.5.   Treatment Compliance

...

Treatment compliance information for abemaciclib will be collected through ~~capsule~~solid oral dosage unit counts at each tumor assessment visit. The estimate of percent compliance will be given by:

$$\text{Percent Compliance} = \frac{\text{Actual cumulative dose taken}}{\text{Expected cumulative dose to be taken}} \times 100$$

The actual cumulative dose taken will be determined based on counting the number of ~~capsules~~ dosage units returned at each visit and subtracting that number from the number of ~~capsules~~ dosage units dispensed. ...

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Attachment 10. **Protocol JPBX Inducers and Strong Inhibitors of CYP3A ~~or~~**
~~**Substrates of CYPs with Narrow Therapeutic Range**~~

The information in this table is provided for guidance to investigators and does not preclude the use of these medications if clinically indicated.

Strong Inducers of CYP3A
Carbamazepine
Dexamethasone[a]
Phenobarbital/phenobarbitone
Phenytoin
Rifapentine
Rifampin
Rifabutin
St John's wort

~~[a] Important note: All patients may receive supportive therapy with dexamethasone, preferably ≤7 days, if clinically indicated.~~

Moderate Inducers of CYP3A
Bosentan
Lenisurad
Modafinil
Primidone
Telotristat ethyl

Strong Inhibitors of CYP3A
Aprepitant
Ciprofloxacin
Clarithromycin
Conivaptan
Diltiazem
Erythromycin
Fluconazole
Itraconazole
Ketoconazole
Nefazodone
Posaconazole
Troleandomycin
Verapamil

[a] Important note: All patients may receive supportive therapy with dexamethasone, preferably ≤7 days, if clinically indicated.

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Cytochrome P450 Substrates with NarrowTherapeutic Range

~~CYP1A2~~	~~Theophylline~~
	~~Tizanidine~~
~~CYP2C9~~	~~Warfarin~~
	~~Phenytoin~~
~~CYP2D6~~	~~Thioridazine~~
	~~Pimozide~~
~~CYP3A~~	~~Alfentanil~~
	~~Astemizole~~
	~~Cisapride~~
	~~Cyclosporine~~
	~~Dihydroergotamine~~
	~~Ergotamine~~
	~~Fentanyl~~
	~~Pimozide~~
	~~Quinidine~~
	~~Sirolimus~~
	~~Tacrolimus~~
	~~Terfenidine~~

Attchment 11.   Protocol JPBX CTCAE 4.03 ~~Diarrhea~~ Definitions for Diarrhea and Interstitial Lung Disease

Interstitial lung disease/pneumonitis will be evaluated in this study using the criteria proposed by CTCAE v4.0 revised: CTCAE 4.03–June 14, 2010: Respiratory, thoracic, and mediastinal disorders.

Respiratory, Thoracic, and Mediastinal Disorders					
Grade					
Adverse Event	1	2	3	4	5
Pneumonitis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated; limiting instrumental ADL	Severe symptoms; limiting self-care ADL; oxygen indicated	Life-threatening respiratory compromise; urgent intervention indicated (e.g., tracheotomy or intubation)	Death
Definition: a disorder characterized by inflammation focally or diffusely affecting the lung parenchyma					

Abbreviation: ADL = Activities of Daily Living.

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